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Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease

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ABSTRACT

Background

Chronic obstructive pulmonary disease (COPD) is a condition associated with high morbidity, mortality and cost to the community. Patients often report symptomatic improvement with long acting beta-2 agonists (LABAs) and anticholinergic bronchodilator medications, both of which are recommended in COPD guidelines. These medications have different mechanisms of action and therefore theoretically could have an additive effect when combined. As these medications are prescribed in COPD as long term therapy, it is important to assemble reliable evidence on their relative and additive effects.

Objectives

To compare the relative efficacy and safety of regular long term use (at least four weeks) of ipratropium bromide and LABA in patients with stable COPD. Comparisons were made between single agents and in combination versus LABAs alone.

Search methods

We searched the Cochrane Airways Group Specialised Register of Trials (July 2008) and reference lists of articles. We also contacted drug companies for relevant trial data.

Selection criteria

All randomised controlled trials comparing treatment for at least four weeks with an anticholinergic agent (ipratropium bromide) alone or in combination with LABA versus LABA alone, delivered via metered dose inhaler or nebuliser, in non-asthmatic adult subjects with stable COPD.

Data collection and analysis

Three review authors independently performed data extraction and study quality assessment. We contacted study authors and pharmaceutical companies for missing data.

Main results

Seven studies met the inclusion criteria of the review (2652 participants). Monotherapy comparison (six studies): There was a significantly greater change in favour of salmeterol in morning PEF and FEV1. There were no significant differences in quality of life, exacerbations, or symptoms. Formoterol appeared to confer some benefits over ipratropium treatment in terms of morning peak flow. Combination

comparison (three studies): There was a significant improvement in post-bronchodilator lung function, supplemental short-acting beta-agonist use and HRQL in favour of combination therapy compared with salmeterol alone.

Authors' conclusions

The available data from the trials suggest that there is little difference between regular long term use of IpB alone and salmeterol if the aim is to improve COPD symptoms and exercise tolerance. However, salmeterol was more effective in improving lung function variables. In terms of post-bronchodilator lung function, combination therapy conferred modest benefits, a significant improvement in HRQL, and reduced supplemental short-acting beta-agonist requirement, although this effect was not consistent. Additional studies are needed to assess the relative effects of combining therapies, using validated subjective measurements, and should consider concordance and the convenience of people having to use different inhaler devices.

PLAIN LANGUAGE SUMMARY

Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease

This review looks at studies that compare the regular use for at least four weeks of different types of bronchodilator medicine (long acting beta-2 agonist medicines and ipratropium) in people with stable chronic obstructive pulmonary disease (COPD, or emphysema/chronic bronchitis).

Chronic obstructive pulmonary disease (COPD) is a condition associated with high morbidity, mortality and cost to the community. Patients often report symptomatic improvement with long acting beta-2 agonists (LABAs) and anticholinergic bronchodilator medications (ipratropium). These medications have different mechanisms of action and therefore theoretically could have an additive effect when combined. As these medications are prescribed in COPD as long term therapy, it is important to know what benefit there are, if any, of prescribing ipratropium alone or as combination therapy over LABAs. Seven studies (2652 participants) were included. Salmeterol was more effective than ipratropium on lung function, but there were no major differences seen between the responses to ipratropium and salmeterol on symptoms. When we compared the combination of these two drugs with salmeterol, combination was superior to salmeterol in terms of quality of life, but the differences between these two treatments on other measurements were small and inconsistent. The findings of the review would not support a general recommendation for the use of ipratropium bromide over a beta-2 agonist alone in COPD, but the combination does confer greater benefit in health status. At this stage, people with COPD should use the bronchodilator that gives them the most improvement in their symptoms. Combination therapy should be considered, but the relative effects of this therapy in relation to other forms of inhaled therapy such as inhaled steroids and tiotropium are unknown. Cost considerations also need to be taken into account as there are considerable variations in price of bronchodilators.

BACKGROUND

This review has been created from an original protocol which was initiated to assess the relative effects of ipratropium bromide and short-acting beta-agonists. However, after the initial registration of this topic, a newer class of long acting beta-agonists (LABA) were developed, and there has been debate comparing the clinical benefit of both treatments in people with severely compromised lung function and daily activity (Appleton 2001).

Despite the lack of major reversibility of airways obstruction, patients often report symptomatic improvement with bronchodilator therapy, and such agents are widely recommended in management guidelines for symptomatic COPD (ATS/ERS 2004; NICE/BTS 2004), even though they do not slow the decline in lung function.

Anticholinergic medicines (such as ipratropium bromide) act on muscarinic receptors, whereas LABAs (salmeterol or formoterol) act via the adrenergic system to cause bronchodilation. These bronchodilators can be delivered in several ways, e.g. by metered dose inhaler, dry powder device or by nebulisation. Some studies demonstrate that ipratropium bromide is at least as effective as short acting beta-2 agonists (Chapman 1991; Matera 1995; Nisar 1992). Ipratropium bromide may be more efficacious than beta-2 agonists in the predominantly elderly COPD patient population, as there may be a decline in response to beta-2 agonists with increasing age, possibly due to reduced receptor numbers (Ullah 1981). In addition, beta-2 agonists potentially have more side effects such as tachycardia and tremor than anticholinergic medicines.

The principal goals of bronchodilator therapy are to alleviate dyspnoea and symptoms, and improve exercise performance. Their main effect is to modify lung ventilatory mechanics and gas exchange. Anticholinergic-mediated bronchodilation occurs predominantly in the large conducting airways and beta-2 agonists act in the peripheral conducting airways. Theoretically, anticholinergic drugs could be more effective in patients with stable COPD than beta-2 adrenergic receptor agonists because of the increased cholinergically- mediated smooth muscle tone which occurs in COPD. It has been suggested that this may be the only reversible component of airways narrowing in COPD (Barnes 1993). Anticholinergics may have additional effects other than bronchodilation in that they may reduce mucous secretion. Also, the action of beta-2 agonists may be impaired due to restricted access of these drugs to their receptors due to bronchoconstriction in the peripheral airways.

The aim of this review was to compare the relative efficacy and safety of regular long term use of shorter-acting anti-cholinergic medications alone or in combination with a long-acting beta-2 agonist compared with the long-acting beta-2 agonist alone, for people with stable COPD.

OBJECTIVES

To compare the relative efficacy and safety of regular long term use (at least four weeks) of ipratropium bromide and LABA therapy in patients with stable COPD.

METHODS

Criteria for considering studies for this review

Types of studies

Studies which are described as randomised controlled trials (RCT) were eligible for inclusion in the review. We restricted the entry criteria to parallel group studies.

Types of participants

Non-asthmatic adults with stable COPD as defined by the British Thoracic Society (BTS 1997). These guidelines specify COPD as a tobacco smoking related, chronic, slowly progressive disorder characterised by airways obstruction (FEV1 < 80% predicted and FEV1/FVC ratio < 70%) which does not change markedly over several months and where the impairment is largely fixed but is partially reversible by bronchodilator or other therapy.

'Stable' was defined as no recent infections, exacerbations, hospitalisation in the past month.

Studies which included participants with severe, concurrent other diseases, including cardiac, liver and renal disease were excluded.

Types of interventions

This review is limited to studies considering ipratropium bromide only, used regularly for at least four weeks in a stated dose, delivered via metered dose inhaler (MDI) or nebuliser, in an outpatient setting, in a randomised comparison with a LABA. Studies were included if they compared:

1) Ipratropium bromide versus LABA.
2) Ipratropium bromide + LABA versus LABA alone

The review protocol specified anticholinergic bronchodilators, and the study duration criteria had originally stipulated eight weeks, but this was revised down to four weeks minimum duration. This review was intended to examine all anti-cholinergic agents (including ipratropium bromide, oxitropium bromide, atropine methonitrate) versus LABA (including salmeterol and formoterol). The comparison with short-acting beta-2-agonists is considered in a separate Cochrane review (Appleton 2006).

The efficacy of tiotropium bromide in comparison with LABA is examined in a separate Cochrane review (Barr 2005).

Types of outcome measures

1) Lung function - including FEV1, FVC, PEF
2) Health status [health related quality of life scores (HRQL)]
3) Dyspnoea scores. These were measured directly, at rest or during exercise, or indirectly by self-report in symptom diaries.
4) Exercise capacity - six minute walk distance (6MWD), shuttle walk test
5) Adverse and haemodynamic effects - blood pressure and pulse rate effects from the medication
6) Use of other medication such as rescue bronchodilators, corticosteroids or theophylline
7) Acute exacerbations

Search methods for identification of studies

Electronic searches

We identified trials using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL, and handsearching of respiratory journals and meeting abstracts. All records in the Specialised Register coded as 'COPD' were searched using the following terms:

(ipratropium or oxitropium or atropine or atrovent or oxivent or respontin) AND (((beta* AND agonist*) AND long*) OR ((beta* AND adrenergic*) AND long*) OR (bronchodilator* AND long*) or salmeterol or formoterol)

Searches are current to July 2008.

Searching other resources

We conducted handsearches of abstracts from meetings of the American and British Thoracic Societies, and the European Respiratory Society. Bibliographies were checked to identify relevant cross-references. We contacted authors and drug companies for relevant trial data. Online databases of unpublished trial summaries were searched (http://ctr.gsk.co.uk; http://www.clinicalstudyresults.org).

Data collection and analysis

Selection of studies

Two authors assessed citations to identify potentially relevant studies. Three authors assessed the full text versions of potential studies to determine if they met the inclusion criteria. Differences were resolved by discussion. Those that met inclusion criteria were assessed for study quality.

Data extraction and management

Three authors independently extracted data for trials and entered this into the Cochrane Collaboration software program (Review Manager). Standard errors (when available) were converted to standard deviations.

Assessment of risk of bias in included studies

We judged the risk of bias for each study (high, low or unclear) based on the process of allocation (generation of allocation schedule and its concealment to investigators/participants).

We assessed trial quality using the following:
(a) Cochrane approach to concealment of allocation
i. Grade A: adequate
ii. Grade B: unclear
iii. Grade C: clearly inadequate

We performed additional assessment using five point scale proposed by Jadad 1996.
1. The study was described as randomised (yes: 1, no: 0).
2. Method of randomisation was described and was appropriate (yes: 1, no: -1).
3. The study was described as double blind (yes: 1, no: 0).
4. The method of blinding was described and was appropriate (yes: 1, no: -1).
5. The was a description of withdrawals and drop outs (yes: 1, no: 0).

Dealing with missing data

We contacted authors and drug companies in an attempt to obtain missing and raw data. In some cases there was no measure of spread of data, although means are known. These trials are listed in MetaView as having n of 1 and in this case these studies are not included in the meta-analysis.

Assessment of heterogeneity

We carried out tests for heterogeneity using the I square statistic.

Data synthesis

Results of the analyses for continuous outcomes are expressed as a weighted mean difference (WMD) together with 95% confidence interval (CI) or a standardised mean difference (SMD) SMDs for outcomes where there was variation in the method of reporting of those outcomes. For dichotomous outcomes, odds ratio (OR) are used.

Sensitivity analysis

If significant heterogeneity was found, (I square > 20%) sensitivity analysis using study quality as a categorising variable was planned. If the heterogeneity was not explained in terms of study quality the following subgroup analyses were to be conducted:

i) Delivery system (e.g. metered dose inhaler versus nebuliser)

RESULTS

Description of studies

Results of the search

We retrieved twenty-six studies (32 references). Of these nineteen were excluded for the following reasons: comparison with placebo and not beta-2 agonist (2), review articles (2), studies were of too short a duration (10), not RCTs (4), study participants had asthma only (1). Seven studies (presented in 13 published and unpublished references) recruiting a total of 2652 participants met the inclusion criteria. Two unpublished studies were identified from the online register of trials by GSK (SMS40314; SMS40315). Unpublished data were available for Mahler 1999 and Rennard 2001. Updated searches were conducted in July 2007 and 2008 but did not identify any new studies for conisderation in the review.

Included studies

For details of individual study characteristics see Characteristics of included studies.

Ipratropium bromide versus long acting beta-2 agonist alone

Salmeterol

Four large studies (two published and two unpublished) comprising 1641 participants were identified which compared the effects of ipratropium bromide (42 mcg) with salmeterol (50 mcg) and placebo. Data from 1365 participants are included in the review (ipratropium N = 682, salmeterol N = 683). All medication was delivered by MDI for 8 to 12 weeks. A history of asthma was an exclusion criterion only in Mahler 1999. In both published studies, participants were stratified and analyses were conducted according to their post-bronchodilator reversibility (FEV1 increase < 12% and 200 mls after albuterol administration). Although baseline reversibility tests were not reported in the unpublished studies,

we have opted to include them in this review and we have performed sensitivity analyses to see whether data from these studies could influence the size and direction of the summary estimates (SMS40314; SMS40315).

Mean baseline FEV1 in Rennard 2001 was 1.22 litres and 1.28 litres in the salmeterol and ipratropium groups respectively. In Mahler 1999, the baseline FEV1 in the salmeterol group was 1.36 litres (42.1% predicted) but it was 1.18 litres (37.0% predicted) in the ipratropium group. This difference between treatment groups was significant (P = 0.016). Current smoking status was not reported. Participants had a mean age of 63 years in both studies and there was a higher prevalence of males in Mahler 1999 (74%) than in Rennard 2001 (63%). Baseline lung function was not reported in SMS40314 and SMS40315.

Formoterol

Two studies were identified which compared formoterol with ipratropium.

Stahl 2002 randomised 183 participants for a 12 week comparison of ipratropium (80 mcg three times daily) with formoterol (18 mcg twice daily) and placebo (using a double dummy design). Measurements reported were health related quality of life (SGRQ scores), lung function, symptom scores, shuttle walking test distance and Borg dyspnoea scores. Unpublished data (standard errors) were obtained for the trial outcomes from one of the authors for the study. Mean baseline FEV1 of the patient group was 33% predicted. Participants in this study had non-reversible airways obstruction as defined as an increase in FEV1< 12% of predicted normal value (and not of baseline) after inhalation of formoterol and ipratropium. Adult asthma was an exclusion criterion in this study. Mean age of participants was 64 years and males comprised 53%.

Dahl 2001 compared two doses of formoterol (12 mcg and 24 mcg) with ipratropium (40 mcg qid) and placebo (using a double dummy design) in 780 participants, over 12 weeks. Standard deviations were unpublished and not able to be obtained from the authors or drug company. Mean baseline FEV1 of the patient group was 1.30 litres or 45% predicted, current smoking ranged from 42 to 52.6%. Current or past diagnosis of asthma was an exclusion criterion. For comparison with the Stahl study, approximately 60% of participants presented with a change in FEV1 < 15% and 200 ml after inhalation of salbutamol. Mean age of participants was 63 years and males comprised 75%.

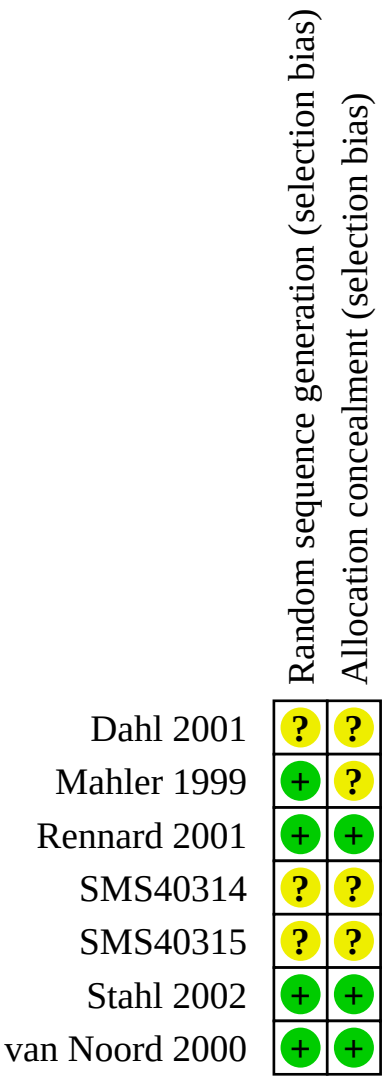
Ipratropium bromide plus long acting beta-2 agonist versus long acting beta-2 agonist

Data for one published (van Noord 2000) and two unpublished studies (SMS40314 and SMS40315) comparing ipratropium in addition to salmeterol versus salmeterol were identified. These studies recruited 991 participants, and assessed treatment for between 8 to 12 weeks. Mean baseline FEV1 of the study population as reported in van Noord 2000 was 1.33 litres. No baseline lung function data were available for the unpublished studies. In van Noord 2000, 57% of people in the combination therapy group were current smokers compared with 49% in the salmeterol group. van Noord 2000 compared MDI delivered salmeterol (50 mcg bid) plus ipratropium (40 mcg qid) with salmeterol (50 mcg bid) and placebo using a double dummy design. In these two studies, participants had no history of asthma, allergic rhinitis or atopy. Participants demonstrated mean FEV1 reversibility of 6% of predicted value, or 13% of baseline.

Risk of bias in included studies

An overview of the risk of bias according to the means of allocating participants to treatment groups is given in Figure 1.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Ipratropium versus long-acting beta-2 agonist

Salmeterol

Using the Cochrane approach to concealment of allocation, Mahler 1999; SMS40314; SMS40315 were rated B and Rennard 2001 was rated A. Using the Jadad scale of study quality assessment, Mahler 1999; Rennard 2001 scored 5, and SMS40314; SMS40315 scored 3.

Formoterol

After correspondence with one of the authors (K Strom), Stahl 2002 was rated A according to the Cochrane approach to concealment of allocation, and using the Jadad scale of study quality assessment, the study scored 5. Dahl 2001 was rated B according to the Cochrane approach to concealment of allocation, and using the Jadad scale of study quality assessment, the study scored 3 because the methods for allocation concealment, and randomisation is unknown and withdrawals were inadequately described.

Ipratropium in combination with a long-acting beta-2 agonist compared to long-acting beta-2 agonist

Using the Cochrane approach to concealment of allocation van Noord 2000 was rated as A, following correspondence with one of the authors (Rutten van Molken), and had a Jadad score of 5.

Other characteristics and methodological criteria

Two studies commented on the number of patients excluded from the trial (van Noord 2000; Dahl 2001). Only one study had an inadequate description of withdrawals and dropouts (Dahl 2001),

and all the studies reported that intention to treat analysis was employed. Only three studies provided a power calculation (Dahl 2001; Rennard 2001; Stahl 2002).

Effects of interventions

In most studies, lung function was the major outcome and was measured in terms of FEV1 and FVC. For each of these lung function parameters, there was a measure of mean pre-dose FEV1 and FVC, mean peak change in FEV1, FVC from the test day baseline and mean area under the FEV1 and FVC curves (AUC) above test day baseline FEV1 and FVC respectively.

Ipratropium bromide versus long-acting beta-2 agonist

Salmeterol studies

Originally, the unpublished data from the non-reversible strata were obtained from GSK and used as a proxy-indicator of non-asthmatic status, but as more recent criteria for the definition of COPD do allow some reversibility, the unpublished data for the overall groups have now been incorporated.

i) Lung Function

Change from baseline in FEV1
There was a significant change in FEV1 favour of salmeterol (MD -0.06 Litres (95% CI -0.11 to 0)).

Area under the FEV1 curve above test day baseline (FEV1 AUC)
There was no significant difference between ipratropium and salmeterol (MD -0.28 (95% CI -0.88 to 0.32)).

Change from baseline in FVC
There was no significant difference between salmeterol and ipratropium (MD 0 (95% CI -0.13 to 0.12)).

Change from baseline in FVC AUC
There was no significant difference between salmeterol and ipratropium (MD 0.64 (95% CI -0.63 to 1.91)

Change from baseline in PEF
There was a significant difference in favour of salmeterol in morning PEF (MD -10.96 (95% CI -16.09 to -5.83). There was no significant difference evening PEF (MD 2.77 (95% CI -2.6 to 8.14).

ii) Health Related Quality of Life- Chronic Respiratory Disease Questionnaire (CRDQ)

CRQ Total score: There was no significant difference between treatments in the improvement from baseline in CRQ Total scores (MD -0.58 (95% CI: -3.50 to 2.35)). However, after 12 weeks of treatment, both IpB and salmeterol resulted in improved Total scores. There was also no significant difference between treatments in the number of people achieving at least a ten unit increase in Total CRQ score (OR: 0.77, 95% CI: 0.54 to 1.11).

Discrete domain differences were unpublished: Dyspnea: MD 0.85 units (95% CI -0.15 to 1.85); Fatigue: MD -0.1 units (95% CI -0.89 to 0.69); Emotion: MD: -0.87 units (95% CI -2.01 to 0.27); Mastery: MD -0.33 (95% CI -1.05 to 0.39).

iii) Dyspnoea Scores

The Transition Dyspnoea Index (TDI), was utilised to measure the change in severity of dyspnoea. There was no significant difference between salmeterol and ipratropium: 0.1 (95% CI -0.38 to 0.59). Post minus pre-test Borg scores showed no significant difference between salmeterol and ipratropium -0.04 (95% CI -0.29 to 0.2).

iv) Symptom scores

Self-assessed day and night-time symptom scores were recorded in daily diaries. There were no significant differences between salmeterol and ipratropium in change from baseline scores for any of the separate daily or nocturnal symptom domains (day shortness of breath: MD -0.04 (95% CI -0.16 to 0.07); day cough: MD -0.04 (95% CI -0.14 to 0.06); day chest tightness: MD -0.05 (95% CI -0.13 to 0.02; nocturnal shortness of breath MD 0.06 (95% CI -0.02 to 0.15); nocturnal cough: MD 0.01 (95% CI -0.08 to 0.1); nocturnal chest tightness: MD 0 (95% CI -0.06 to 0.05); night awakenings: MD 0.06 (95% CI -0.03 to 0.15)).

v) Exercise Capacity

There was no significant difference in the change from baseline in metres walked during six minute walk tests (MD 10.47 (95% CI -1.24 to 22.19).

vi) Rescue bronchodilator use

No significant difference was demonstrated in the number of daytime puffs of salbutamol (MD 0.34; 95% CI -0.20 to 0.88) between salmeterol and IpB treated groups over the 12 week study duration.

vii) Number of participants experiencing exacerbations/lack of efficacy

There were no significant differences between treatment groups in the number of participants experiencing one or more exacerbations of COPD (Peto OR 1.23 (95% CI 0.84 to 1.80), or in the number of participants who withdrew due to a lack of efficacy (Peto OR 1.04 (95% CI 0.61 to 1.79).

viii) Medication related adverse events and haemodynamic effects

There was no significant difference between salmeterol and ipratropium in the number of participants with adverse events (Peto OR 1.08 (95% CI 0.75 to 1.57)). There was no significant difference between treatment groups in the number of participants who withdrew due to adverse events (Peto OR 1.44 (95% CI 0.82 to 2.52)).

Formoterol studies

Two studies (Dahl 2001; Stahl 2002) determined the effectiveness of IpB in comparison with formoterol (and placebo), delivered by MDI, over three months. The Dahl 2001 study group consisted of non-asthmatic COPD patients and the formoterol dose was 12 mcg (F12) and 24 mcg (F24), however the Stahl 2002 study group consisted of participants with FEV1 reversibility of less than 12% predicted normal value, testing the 24 mcg dose only. Unpublished SD data was unobtainable for the Dahl study which prevented meta-analysis.

i) Lung Function

Stahl 2002 reported no significant difference between IpB and formoterol in terms of FEV1 or FVC using multiplicative analysis of variance models.

Dahl 2001 reported statistically significant treatment differences for the normalised FEV1 area under the curve at week 12: F12-IpB = 0.086 litres, (P = 0.001; F24-IpB = 0.057 litres, (P = 0.024. These differences did not exceed the 120 ml improvement deemed to be

clinically relevant. After the last dose of trial medication, in terms of mean FEV1 over 12 hours, formoterol was statistically better than ipratropium at most time points but F12 yielded clinically meaningful improvements over IpB (i.e. at least 120 ml at 5, 15, 30 min, and 1,2,4, and 5 hours.

Stahl 2002 reported that morning pre-medication PEF was significantly higher in the formoterol group compared to IpB (difference = 8.2 litres/min; 95% CI 0.5 to 15.8, P = 0.04. There were no significant differences between treatments for evening PEF values. Dahl 2001 reported that in terms of morning pre-medication PEF, formoterol was more effective than IpB, F12-IpB = 23.8 litres/min, (P = 0.001 F24-IpB = 23.8 litres/min, (P = 0.001).

ii) Health Related Quality of Life (St Georges Respiratory Questionnaire, SGRQ)

Stahl 2002 reported no significant differences between treatment groups in the change from baseline in Total SGRQ. Of the sub-domains, only the Symptoms domain showed a significant difference between treatment groups- IpB treatment was associated with a 5.7% units increase over formoterol (i.e. 5.7 units).

Dahl 2001 reported that F12 produced a statistically significant improvement over IpB in Total SGRQ score, which approached clinical significance (reduction in score of 3.79 units). Clinically significant treatment differences in favour of F12 for the Activity (4.25 unit reduction) and Impacts (4.04 unit reduction) domain scores were also reported.
Mean changes in score from baseline within treatments were not reported, however, in terms of the difference between mean scores at baseline and at the mean scores at the end of the study, F12 was associated with a reduction in score of at least 4.0 units for the Total, Symptoms, Activity, and Impacts domains, whereas F24 was associated with clinically relevant reductions in the Total and Symptoms domains only and IpB treatment was associated with a significant reduction in the Symptoms domain only.

iii) Dyspnoea Scores

Stahl 2002 reported no significant differences between treatment groups in terms of day time or night-time breathlessness and cough.

Dahl 2001 reported that F12 produced a significant improvement over IpB in Total diary symptom scores (P = 0.009).

iv) Exercise Capacity

Stahl 2002 no significant difference between IpB and formoterol in the shuttle walk test distance.

v) Haemodynamic effects, adverse events

There were no significant changes on ECG in blood pressure or pulse rate and there were no significant differences in the frequency of adverse events between treatments (Dahl 2001; Stahl 2002).

vi) Exacerbations

In Dahl 2001, the percentage of "bad days" (at least two individual symptom scores of two or more and/or a reduction in peak flow from baseline of 20%) was significantly lower with F12 and F24 treatment compared with IpB (P < 0.001 and P = 0.01 respectively). There was no difference in the number of days additional therapy was required for COPD exacerbations between treatments. There were two hospitalisations in each of the F12 and F24 groups and six in the IpB treated participants.

Ipratropium plus long-acting beta-2 agonist versus long-acting beta-2 agonist

Three studies reported outcomes relating to this comparison (SMS40314; SMS40315; van Noord 2000).

i) Lung Function

Pooled analysis was possible for one outcome from the unpublished studies.

Summary FEV1 AUC
There was a significant difference in favour of combination (MD 1.38 Litres (95% CI 0.98 to 1.77), two studies, N = 720)

van Noord 2000 reported the following findings for lung function:
Pre-bronchodilator lung function: After 12 weeks of treatment, no significant improvements were demonstrated in mean morning PEF between treatment groups. The combination therapy was associated with a significantly larger change from baseline in evening PEF (P < 0.1).

Post- bronchodilator lung function: There were significant differences between treatments favouring the combination in the mean increase over baseline in percent predicted FEV1: IpB + salmeterol = 8% predicted versus salmeterol = 5% predicted (P < 0.01).

A significant difference between treatments favouring the combination was also seen for FVC. The mean increase for IpB + salmeterol was 12% predicted versus salmeterol treatment alone, 7% predicted (P < 0.01).

ii) Health Related Quality of Life

CRDQ
In participants receiving combination therapy, statistically significant changes from baseline were demonstrated for the CRQ Total domain score (MD 0.4, 95% CI 0.1 to 0.7) and the Fatigue score. In participants receiving salmeterol, a statistically significant reduction was seen for the Emotions domain. These changes were not regarded as clinically significant however. No significant within or between group improvements were demonstrated in the CRQ Dyspnoea and Mastery domains.

The authors also reported significant differences in the proportions of participants achieving a clinically relevant change in the Total CRQ score: IpB + salmeterol = 40%, salmeterol = 13%.

SGRQ
There was a significant difference in the mean change in total SGRQ in favour of combination therapy (2 units (95% CI -3.49 to 0.52), three studies, N = 837).

Data on other individual domains (i.e. symptoms, impacts and activity) were available only from van Noord 2000. The SGRQ Symptoms domain was the only domain showing significant improvement in the combination therapy group (reduction of 8.1 units) compared to baseline. This is regarded as being moderately clinically significant (four units being the minimal significant change). The scores on the Symptoms domain with combination therapy also showed statistically significant differences compared

to salmeterol treatment (-8.1 versus 1.4, P = 0.02) No statistical or clinically significant changes in score from baseline were demonstrated by the salmeterol treated group.

The activities and impacts domains showed no significant changes from baseline or between treatment differences.

There were no significant differences in the proportions of participants achieving a clinically relevant change (4 units) in the total SGRQ score: combination (23%), salmeterol (24%).

iii) Dyspnoea Scores

Pooled analyses for TDI at endpoint and change in symptoms were available for the two unpublished studies.

TDI at endpoint
There was a significant difference in favour of combination therapy compared with salmeterol (MD: 0.85 (95% CI 0.46 to 1.24), N = 761. Although statistical heterogeneity was high for this outcome (I square 67.3%), the effect remained significant with random effects modelling (MD 0.85 units (95% CI 0.16 to 1.54).

Change in symptom scores
There was no significant difference in the mean change in symptom scores (MD -1.89 (95% CI -11.11 to 7.34), N = 815.

van Noord 2000 reported no significant changes from baseline in self-reported daytime symptom scores at 12 weeks between treatment group as both groups had significantly less symptoms compared with baseline scores (P < 0.01). Mean scores were reduced to 1.3 for the combination, and 1.4 for salmeterol compared to 2.0 at baseline for both groups.

iv) Rescue bronchodilator use

Pooled analyses for mean change in supplemental beta-agonist use were available for the two unpublished studies.

There was a significant reduction in the number of puffs of supplemental beta-agonist per day in favour of combination therapy (-0.67 puffs/day (95% CI -1.11 to -0.23). Although there was significant statistical heterogeneity for this outcome (I square 41.7%), random-effects modelling still gave a significant pooled effect (-0.64 puffs/day (95% CI -1.22 to -0.06).

van Noord 2000 reported no significant difference between groups in the percentage of days or nights without additional salbutamol use over the 12 week study duration (P = 0.5).

v) Number of participants experiencing exacerbations

van Noord 2000 reported no significant difference between treatment groups in the number of subjects experiencing an exacerbation of COPD over the 12 week study duration: IpB + salmeterol n = 6 (13%), salmeterol n = 11(23%).

vi) Adverse events

There was no significant difference between combination and salmeterol in the incidence and nature of possible and probably drug-related adverse events between treatment groups (Peto OR 1.08 (95% CI 0.83 to 1.4), three studies, N = 936).

DISCUSSION

We have analysed evidence from seven studies in this review. The information available on the methodological design of the studies suggested that they were of high quality. The disparate reporting of outcome and limited availability of outcome data from these studies have limited the number of pooled analyses that we have been able to conduct. Evidence from these studies indicates that whilst salmeterol led to a greater improvement in one lung function variable, the effect was not consistent. The difference between salmeterol and ipratropium as monotherapies on subjective outcome was not significant. The combination of ipratropium and salmeterol was significantly more effective than salmeterol alone. There was evidence of improved quality of life with combination therapy over salmeterol alone, and reduced requirement for supplemental short-acting beta-agonist.

Effects of ipratropium bromide alone versus a long-acting beta-2 agonist

Pooled analysis for a limited number of outcomes of all four studies which measured effectiveness of ipratropium in comparison with salmeterol (and placebo) over 12 weeks (Mahler 1999; Rennard 2001; SMS40314; SMS40315), was possible after unpublished data were identified and analysed. This showed a benefit of salmeterol over ipratropium on certain lung function outcomes (change in morning PEF, FEV1) but no significant differences on subjective, validated measurements of health status or symptoms. The likelihood of study withdrawal due to adverse events or lack of efficacy was not significantly different between the two therapies, and the frequency of any adverse event was also not significantly different.

Although the 12-week data significantly favoured salmeterol over IpB, Mahler 1999 reported that at week 12, the FEV1 response over the pretreatment baseline to a single dose of salmeterol over 12 hours was not significantly different to the response to two doses of ipratropium except at time = 0, 4 and 6 hours. The differences at the 4 and 6 hour time points probably reflect the short duration of action of ipratropium and comparisons between salmeterol and the long-acting tiotropium are probably more appropriate. The treatment difference of approximately 150 ml at time zero- i.e. day 84 trough compared to the day 1 FEV1 baseline suggests a clinically meaningful benefit of salmeterol. This conferred few other benefits. The four studies did not show a significant difference in Transition Dyspnoea Index scores. However, Mahler 1999 and Rennard 2001 found no difference between treatments in six minute walk distance or post walk dyspnoea (Borg scores) and haemodynamic effects.

Two studies have compared the effects of formoterol and IpB but pooled analysis was not possible as the missing data were not obtainable. Dahl 2001 compared formoterol at 12 and 24 mcg, whereas Stahl 2002 compared the 24 mcg dose only with IpB. Both studies showed that the drugs were comparable in terms of the adverse events and haemodynamic effects, and formoterol treatment was associated with statistically significant higher morning PEF compared with ipratropium. Comparisons of the results of the studies show inconsistencies with the 24 mcg formoterol dose with respect to lung function, and SGRQ scores. Considered in isolation, and therefore with caution, the findings from Dahl 2001 suggest that the 12 mcg dose of formoterol has benefits over ipratropium. These inconsistencies highlight the need

for meta-analyses to explore the size and consistency of an effect across different studies.

There was some variation in the inclusion criteria between these studies. Participants in Stahl 2002 had no history of adult asthma and exhibited bronchodilator reversibility of FEV1 < 12% of predicted normal value after inhalation of formoterol and ipratropium. This allows for a relatively large reversibility however, but it is possible that the limited benefits in the study may reflect this inclusion criteria. Participants in Mahler 1999 and Rennard 2001 were stratified and analyses were conducted according to their post-bronchodilator reversibility of FEV1 (= 12% and = 200 mls). There is clearly a body of opinion (Anthonisen 1986; Calverly 2003) that suggests that a bronchodilator response should not be used as a criterion on which to base decisions about long-term treatment of COPD patients with bronchodilator drugs. However, there is also evidence emerging from studies that compare the effects of bronchodilators in participants with and without bronchodilator responses and it is apparent that firstly non-responsive participants comprise a significant proportion of the COPD population (around 50% of the recruited patients) (Mahler 2002; Rossi 2002; Tashkin 2003) and while a non-responsive fraction experience some significant benefits, the benefits are in the order of half the magnitude of those experienced by the responsive patients (Mahler 1999; Rossi 2002; Mahler 2002; Tashkin 2003). Given that the clinical benefits may become marginal for the non- or poorly responsive group, it is arguable that there is a need to determine the benefits in this and other sub-groups of COPD (based upon severity for example).

Effects of ipratropium bromide in combination with a long-acting beta-2 agonist

To date, one published and two unpublished studies have been conducted to determine the benefits of IpB-salmeterol combination therapy versus salmeterol alone in people with COPD. While no benefit of either treatment was observed in participants' morning pre-medication PEF values, clinic measured pre-bronchodilator lung function tests may have provided more accurate data of the effect of treatment. Combination therapy (van Noord 2000) resulted in significantly higher increases in post-bronchodilator lung function compared with the salmeterol treatment which may confer some clinical benefit (mean difference % predicted FEV1: 3%, approximately 130 ml, and mean difference in FVC: 5%). The post-bronchodilator benefits suggest a possible role for combination therapy in subjects with relatively fixed airways obstruction (mean FEV1 reversibility was 13%). However the treatments were comparable in terms of symptom reduction, rescue salbutamol use, and frequency of adverse events and COPD exacerbation rate and therefore the cost of the combination must be considered in light of this.

The quality of life data available indicate that there was a significant difference in the change in total SGRQ score in favour of combination therapy. Given that the comparison was between active treatments, this difference may be of some value when making a choice between these two therapies. The CRQ data available in van Noord 2000 showed no clinically relevant improvements (0.5 units per question per domain) in any domain with either treatment. There were however, a significantly higher proportion of participants on combination therapy (approximately 39%) achieving clinically meaningful improvements in the Total CRQ score, compared with salmeterol therapy (13%). Furthermore, the prevalence of significant worsening of scores was 13% in the combination group and 26% in the salmeterol group and 21% in the placebo group. The deterioration in the CRQ Total score in the salmeterol group is difficult to explain given that the adverse event rate was similar across treatment groups and that salmeterol has been previously shown to be well tolerated (Boyd 1997; Ulrik 1995). Until more studies are available which may enable meta-analyses, these data suggest that treatment should be targeted at those who demonstrate improvement in HRQL using validated disease specific instruments. It is also arguable that 12 weeks therapy is not long enough to detect HRQL changes in stable patients who, as the author claims, are being optimally managed (van Noord 2000). The small improvements in lung function obtained with combination therapy over LABA treatment may correlate with the significant effects in the SGRQ score. However, the lack of an effect and the low statistical power for the CRQ scores need to be interpreted with caution as they are drawn from a single study. Additional studies in this area would help to explore the effects of these drugs on different quality of life instruments.

It is difficult to draw conclusions about the relative efficacy of IpB alone or in combination with salmeterol or formoterol versus the LABA alone. Generally, objective benefits such as an increase in FEV1 of around 150 ml occurred in the absence of subjective benefits such as improved quality of life or symptom scores. When objective improvements conferred subjective improvements, this was the result of one study and the conclusions are limited. The additional cost of adding salmeterol or formoterol to ipratropium becomes an important issue to consider. Although the impact of the costs in terms of "who pays" varies between countries, and the costs of the drugs themselves will vary, it is clear that there are significant additional costs of ipratropium and LABA treatment over SABA treatment. In Australia, for example, the predicted government costs of supplying one month of treatment (MDI delivered) of salmeterol and ipratropium are eight fold and seven fold respectively over the cost of one months salbutamol supply (Cwealth of Aust 2000). Nebulised therapy is more costly again and therefore the significant additional costs require consideration when benefits are of marginal clinical significance. This again highlights the need to identify individual patients who do benefit from these therapies.

A role for "N = 1 randomised trials" to identify patients who actually benefit from anticholinergic therapy has been suggested (van Weel 1998). Patient preference, acquired with methodological validity, may be valuable to determine which drug or drug combination is appropriate for which patient. The relevance of patient preference has been demonstrated in a randomised double-blind crossover study (Blosser 1995) comparing the effects of ipratropium 36 mcg qid and salbutamol 180 mcg qid for seven days in 15 participants with COPD, which reported that the mean FEV1 after seven days therapy was not significantly different between the treatments. No difference in exercise tolerance or dyspnoea scores were reported at the end of the treatment interval. However, in a subjective evaluation of the treatments, seven participants favoured ipratropium, seven favoured albuterol and one had no preference. Importantly, only 5 of the 15 participants preferred the drug to which they showed greatest reversibility in FEV1. As this review has shown that there is little objective difference between any of the bronchodilator strategies, therapy should be targeted to those patients shown to benefit from it.

There is currently no evidence that bronchodilator therapy reduces the rate of decline in lung function which occurs in COPD (Anthonisen 1994), although there is some evidence of a significant change in FEV1 over a short term (Appleton 2006). According to a review of COPD management guidelines (Ferguson 2000), guidelines are inconsistent in their recommendations for the pharmacological management of COPD. While all recommend inhaled bronchodilators as first-line therapy, the BTS and ERS do not recommend preferential use of anticholinergic agents over beta-2 agonist as initial therapy (ATS/ERS 2004; NICE/BTS 2004). GOLD suggests that the choice between drugs and their combination depends upon availability of the drug and each patient's response but claims that long-acting bronchodilators are more effective than short-acting bronchodilators (GOLD 2003). Recently, the Global Initiative for Chronic Obstructive Pulmonary Disease Workshop Report (updated 2004) recommended the use of the longer acting anticholinergic medication- tiotropium for moderate to very severe COPD (GOLD 2004). All guidelines discuss the value of combination therapy but Pauwels 2000 states that there is no clear indication whether either type of agent or a combination of the two is the first choice. However, where implications for health care resources are considered, guidelines need to recommend a safe and cost-effective approach to the pharmacological management of COPD in the absence of evidence of clear benefits of one agent over another.

Given the general acceptance and recommendation of IpB/beta-2 agonist combination therapy for the treatment of patients with COPD, the superiority of the type of a LABA remains to be determined. To date only one study (D'Urzo 2001), a randomised, double blind, cross-over trial, has been reported, comparing IpB (40 mcg qid) plus formoterol (12 mcg bd) and IpB plus salbutamol (200 mcg qid). Evaluation after 3 weeks of treatment demonstrated statistically significant increases in mean pre-bronchodilator PEF (12 litres/min) and FEV1 (0.120 litres) values with the formoterol/ipratropium combination compared with the salbutamol/ipratropium combination. Post-bronchodilator FEV1 values were also shown to be significantly increased with the formoterol combination (in the order of 0.150 litres). These marginal clinical benefits will need to be weighed against the additional costs of adding a long-acting beta-2 agonist to ipratropium.

The findings of this review should be seen in a general context and not limited to the consideration of single variables. There is accumulating evidence which suggests that spirometric measurements of FEV1 and FVC may not be the best measures of bronchodilator response in COPD, and there is evidence of a relationship between exacerbations and the deterioration in health-related quality of life in COPD (Spencer 2004). The findings on some of the subjective outcomes, whilst apparently unsupported by the lung function data, do nevertheless give some guidance on the use of these bronchodilating agents. The role of spirometry in evaluating therapeutic responses has been reviewed (O'Donnell 2000). In advanced COPD, exertional dyspnoea has been correlated with the level of dynamic lung hyperinflation (DH) (Belman 1996; O'Donnell 1997; O'Donnell 1998) as measured by inspiratory capacity (IC). Furthermore, a RCT using cross-over study design with three week treatment arms of ipratropium and placebo (O'Donnell 1999) showed that of the available spirometric parameters which indirectly measure reduced lung hyperinflation, IC correlated better than expiratory flow measurements, with reduced dyspnoea and improvements in exercise tolerance. An increases in IC of 10% predicted (0.3 L) was associated with a significant increase (> 25%) in exercise endurance time. Perhaps, most significantly, the improvements in IC and exercise tolerance after ipratropium treatment occurred in a proportion of participants (31%) who showed little or no improvement in FEV1 (< 10% predicted). Future critical evaluation of the benefits of bronchodilator therapy will require the incorporation of measurements of lung hyperinflation in spirometric assessments, in addition to measures of symptoms, exercise tolerance and HRQL and longer trial duration to detect critical events such as hospitalisations due to exacerbations.

AUTHORS' CONCLUSIONS

Implications for practice

Results from the trials included in the review indicate that when assessed as a monotherapy, salmeterol confers benefit in terms of lung function over ipratropium bromide, but the effects on subjective measurements are more equivocal. While studies showed that ipratropium and long-acting beta-2 agonists yielded benefits, there is currently insufficient evidence to make conclusions about the superiority of ipratropium versus either salmeterol or formoterol, given the inconsistent results reported across studies. There was evidence of benefit of ipratropium in combination with salmeterol, with significant improvements in post-bronchodilator FEV1, in addition to some HRQL benefits, and a reduced requirement for supplemental short-acting beta-agonist over salmeterol alone.

Implications for research

The relative value of ipratropium therapy alone or in combination with long acting beta-2 agonists needs still to be determined in studies which measure outcomes such as measures of inspiratory capacity or dynamic hyperinflation in combination with other measures such as exercise tolerance, dyspnoea scores, HRQL and effects on exacerbation rates. Studies should incorporate measures of health utilisation measures and need to be of longer duration to capture effects on exacerbation rates. The important issue of patient preferences need to be considered in future studies, the convenience of having to manipulate more than one inhaler device (with potentially different dosing regimens), as does the question of how therapy is escalated in COPD. It is arguable however that given the emergence of the long-acting anticholinergic tiotropium on to the market, future studies should focus on the evaluation of this therapy using relevant outcomes, for long term use in COPD, including comparisons with existing effective therapies. Its relative cost effectiveness also needs to be considered.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dahl 2001

Study characteristics	
Methods	RCT: Parallel group study. Randomisation: unclear Aloocation concealment: unclear. Blinding: double blind Excluded: described. Withdrawals: inadequately described. Trial duration: 12 weeks. Power calculation given. Intention to treat analysis. Jadad Score: 3
Participants	Setting: International, multi-centre study. Participants: 780 (Form12: 194; Form24: 192; IpB: 194; placebo: 200). Mean age: 64 yrs; male:female (%): 75:25. Mean baseline FEV1: 1.30 litres (45% predicted). Inclusion criteria: >/ = 40 years of age, stable COPD, FEV1 < 70% predicted, FEV1/VC < 88% predicted for men and < 89% predicted for women, current or ex-smokers with > 10 year pack history of smoking, day or night-time symptoms present on at least 4 of last 7 days of run-in. Exclusion criteria: current/past diagnosis of asthma, need for long term oxygen therapy, respiratory tract infection in past month, initiation or discontinuation of inhaled corticosteroids, or change in daily dose in previous month, treatment with oral corticosteroids in the previous month, current treatment with theophylline, anticholinergics, long-acting beta-2 agonists.
Interventions	1) formoterol 12mcg b.i.d. (& IpB placebo q.i.d.) 2) formoterol 24 mcg b.i.d. plus placebo matching IpB q.i.d. 3) ipratropium q.i.d. plus placebo matching formoterol b.i.d. 4) placebo IpB q.i.d plus placebo form b.i.d. Inhaler device: DPI
Outcomes	FEV1 AUC (0-12hr hr); FEV1; Normalised FEV1 AUC; Pre-dose FEV1;

Dahl 2001 *(Continued)*

	FEV1 at all time points during 12 hour spirometry; Morning pre- medication PEF; Number puffs rescue medication; COPD symptoms (ability to perform usual activities, dyspnoea on rising and over previous 24 hr, cough, waking at night with symptoms, sputum production); Quality of life (SGRQ); COPD exacerbations.
Notes	Unpublished standard errors/deviations sought from author- no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available

Mahler 1999

Study characteristics

Methods	RCT: Parallel group study. Randomisation: computer generated. Allocation concealment: unclear. Blinding: double blind. Excluded: not described. Withdrawals: described. Baseline characteristics: comparable. Power calculation: not given. Intention to treat analysis. Jadad Score: 5
Participants	Setting: USA, multi-centre study. Participants (only participants with non-reversible obstruction in 2 of 3 treatment arms included in review): 95 (Sal: 48; IpB: 47). Mean age: 63 years; male:female (%): 74:26. Mean FEV1: 1.19 litres or 40% predicted, no range given. Inclusion criteria: > 10 year pack history of smoking, > 35 years of age, FEV1 < 65% predicted, FEV1/FVC < 70 %, SOB on mild exertion at baseline using modified MRC Dyspnoea scale. Exclusion criteria: history of asthma, other respiratory disease, significant concurrent disease, change in medication or unstable respiratory status within 4 weeks prior to screening, oxygen therapy other than nocturnal use.
Interventions	1) salmeterol 42mcg b.i.d. (& IpB placebo q.i.d.) 2) ipratropium 36mcg q.i.d. (& Sal placebo b.i.d.) 3) placebo Sal b.i.d. & placebo IpB q.i.d. Inhaler device: MDI
Outcomes	FEV1 and FVC over 12 hours; Dyspnoea; Six minute walk test (Borg scores for dyspnoea); Day and night-time symptom scores; Supplemental albuterol use; Time to first COPD exacerbation; Quality of life (CRDQ);

Mahler 1999 *(Continued)*

	Adverse events
Notes	No SDs published, sought from authors and obtained from Glaxo-Wellcome. FEV1 reversibility (% baseline FEV1) mean (SD): salmeterol: 9.4(9.0) ipratropium: 12.2(7.5)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Information not available

Rennard 2001

Study characteristics

Methods	RCT. Parallel group study. Randomisation: computer generated. Allocation concealment: adequate. Blinding: double blind. Excluded: not described. Withdrawals: described. Baseline characteristics: comparable. Power calculation: not given. Intention to treat analysis. Jadad Score: 4
Participants	Setting: USA, multi-centre study. Participants: 108 (Sal: 54; IpB: 54). Mean age: 63 years. Mean FEV1: 1.15 litres or 41% predicted, no range given. Inclusion criteria: ATS criteria; > 10 year pack history of smoking, > 35 years of age, FEV1 < 65% predicted, FEV1/FVC < 70 %, SOB on mild exertion at baseline using modified MRC Dyspnoea scale. Exclusion criteria: history of asthma, other respiratory disease, significant concurrent disease, change in medication or unstable respiratory status within 4 weeks prior to screening, oxygen therapy other than nocturnal use.
Interventions	1) salmeterol 42mcg b.i.d. (& IpB placebo q.i.d.) 2) ipratropium 36mcg q.i.d. (& Sal placebo b.i.d.) 3) placebo Sal b.i.d. & placebo IpB q.i.d. Inhaler devices: MDI
Outcomes	FEV1 and FVC over 12 hours; Dyspnoea; Six minute walk test (Borg scores for dyspnoea) Day and night time symptom scores; Supplemental albuterol use; Time to first COPD exacerbation; Quality of life (Chronic Respiratory Disease Questionnaire (CRDQ)); Adverse events.
Notes	Unpublished Glaxo-Wellcome clinical trial data: SLGA4004. Published as Rennard 2001. FEV1 reversibility: IpB: 10(8.7)% salmeterol: 9.8(7.6)%

Rennard 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Third party randomisation

SMS40314

Study characteristics

Methods	RCT. Parallel group study. Randomisation: not clear. Blinding: double blind, double dummy. Allocation concealment: unclear. Excluded: not described. Withdrawals: described. Trial duration: 8 weeks. Baseline characteristics: comparable. Power calculation: 200 participants in active treatment groups to detect a significant difference of 1.2 L-hours in FEV1 AUC. Intention to treat analysis. Jadad Score: 3
Participants	Setting: 55 centres in USA. Participants: 731 (Sal: 205; Placebo: 108; Sal/IpB: 213; IpB: 205). Mean age: 64-65 years FEV1: 1.25-1.33 (42% predicted) Inclusion criteria: M/F >/= 40 years; diagnosis of COPD; >/= 20 pack years; FEV1/FVC ratio of < 0.7; FEV1 >/= 0.7L & </= 65% predicted; Exclusion criteria: concurrent use of long acting beta agonists, anti-leukotrienes, xanthine or anti-cholinergic therapy; corticosteroids > 10 mcg per day.
Interventions	1) salmeterol 42mcg b.i.d. (& IpB placebo q.i.d.) 2) ipratropium 36mcg q.i.d. (& Sal placebo b.i.d.) 3) placebo Sal b.i.d. & placebo IpB q.i.d. 4) ipratropium 36mcg q.i.d. (&Sal 42mcg b.i.d.) Inhaler device: MDI
Outcomes	FEV1 AUC; Dyspnoea; Supplemental SABA usage; Quality of life (SGRQ); Adverse events; Withdrawals.
Notes	Unpublished study downloaded from ctr.gsk.co.uk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available

SMS40314 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information not available

SMS40315

Study characteristics

Methods	RCT: Parallel group study. Randomisation: not clear. Blinding: double blind, double dummy. Allocation concealment: unclear. Excluded: not described. Withdrawals: described. Trial duration: 8 weeks. Baseline characteristics: comparable. Power calculation: 200 participants in active treatment groups to detect a significant difference of 1.2 L-hours in FEV1 AUC. Jadad Score: 3
Participants	Setting: 56 centres in USA Participants: 735 (Sal: 211; Placebo: 105; Sal/IpB: 213; IpB: 206). Mean age: 63.5 years; FEV1: 1.33L (43% predicted). Inclusion criteria: M/F >/= 40 years; diagnosis of COPD; >/= 20 pack years; FEV1/FVC ratio of < 0.7; FEV1 >/= 0.7L & </= 65% predicted; Exclusion criteria: concurrent use of long acting beta agonists, anti-leukotrienes, xanthine or anti-cholinergic therapy; corticosteroids > 10 mcg per day.
Interventions	1) salmeterol 42mcg b.i.d. (& IpB placebo q.i.d.) 2) ipratropium 36mcg q.i.d. (& Sal placebo b.i.d.) 3) placebo Sal b.i.d. & placebo IpB q.i.d. 4) ipratropium 36mcg q.i.d. (&Sal 42mcg b.i.d.) Unclear inhaler device.
Outcomes	Quality of life (SGRQ); FEV1 AUC; Symptoms; Supplemental medication usage; Adverse events; Withdrawals.
Notes	Unpublished study downloaded from ctr.gsk.co.uk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available

Stahl 2002

Study characteristics

Stahl 2002 *(Continued)*

Methods	RCT: Parallel group study. Randomisation: computer generated. Allocation concealment: adequate. Blinding: double blind (identical canisters). Excluded: not described. Withdrawals: described. Trial duration: 12 weeks. Baseline characteristics: comparable. Power calculation: given. Intention to treat analysis. Jadad Score: 5
Participants	Setting: Sweden, multi-centre study. Partricipants: 183 (Form: 61; IpB: 62; Pla: 60). Mean age 64 years; mean FEV1: 33% predicted, 0.84 litres. Male/female (%): 53:47. Inclusion criteria: 40-75 years old, current or ex-smokers with at least 10 pack year smoking history, stable disease, FEV1 < 60% predicted, FEV1/FVC < 70 %. Reversibility < 12% predicted normal FEV1 after formoterol or ipratropium bromide. PaO2 at rest > 7.3 kPa. Reduced exercise capacity due to dyspnoea on exertion. Exclusion criteria: patients with adult asthma or on long term oxygen therapy.
Interventions	1) formoterol 18mcg b.i.d (& IpB placebo t.i.d.) 2) ipratropium bromide80 mcg t.id. (& Form placebo b.i.d.) 3) placebo IpB t.i.d. and placebo Form b.i.d. Inhaler device: Form: turbuhaler; IpB: MDI
Outcomes	Shuttle walking test distance; Dyspnoea; Quality of life (SGRQ); FEV1; FVC; Day and night symptom scores; Rescue medication use; Recorded daily in a diary; Adverse events.
Notes	Unpublished data and details of allocation concealment and randomisation supplied by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Third party randomsiation

van Noord 2000

Study characteristics

Methods	RCT: Parallel group study. Randomisation: computer generated. Allocation concealment: adequate. Blinding: double blind, double dummy. Excluded: described.

van Noord 2000 *(Continued)*

	Withdrawals: described. Trial duration: 12 weeks. Baseline characteristics: comparable Power calculation: not given. Intention to treat analysis. Jadad Score: 5
Participants	Setting: Netherlands, multi-centre study. Participants: 144 (Sal: 47; Sal & IpB: 47; Pla: 50). Mean age: 63.8 years Male:female (%): 87:13. Mean baseline FEV1: 1.33 Litres or 44% predicted. Range not given. Current smokers: 49-58%. Inclusion criteria: current/ex-smokers, > 40, < 75 years; FEV1 > 40%, < 65% predicted after inhalation of salbutamol; symptoms on mild exertion on > 4/7 days during run-in period; ex-smokers stopped smoking > 6 months prior to run-in. Exclusion criteria: history of asthma; allergic rhinitis; atopy; other respiratory disease; significant concurrent disease; respiratory tract infection or change in medication within 6 weeks commencement of study; oxygen therapy.
Interventions	1) salmeterol 50 mcg b.i.d. (& IpB placebo q.i.d.) 2) ipratropium 40mcg q.i.d. (& Sal placebo b.i.d.) 3) placebo Sal b.i.d. & placebo IpB q.i.d. Inhaler device: MDI.
Outcomes	Airways resistance (Raw); Airways conductance (sGaw); FEV1; FVC; Symptoms; PEF; Supplemental SABA usage; Number of participants with exacerbations of COPD; Adverse events.
Notes	Mean data for FEV1, FVC, PEF extracted from graphs. Allocation concealment confirmed through correspondence with Dr Rutten van Molken.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Third party randomisation

AUC: area under the curve; b.i.d.: twice daily; CRDQ: Chronic Respiratory Disease Questionnaire; DPI: dry powder inhaler; FEV1: forced expiratoary volume; FVC: forced vital capacity; MDI: metered dose inhaler; q.i.d.: four times daily; MRC: Medical Research Council; RCT: randomised controlled trial; SGRQ: St George's Respiratory Questionnaire; SOB: shortness of breath; t.i.d.: three times daily

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bauer 1975	Comparison of ipratropium bromide and placebo.

Study	Reason for exclusion
Brown 1984	Time course study over 5 hours on three separate days.
Dejaegher 1984	Time course study over seven hours, conducted on two days, in patients with reversible airways obstruction.
Disse 1999	Review article.
Heimer 1991	Time course study over one hour.
Hidalgo 1983	Time course study on one day.
Kheir 1993	Time course study over six hours, on three days.
Khristoliubova 1999	Not a randomised controlled trial
Lees 1980	Time course study on three separate days.
Leitch 1978	Short duration study.
Lien 1980	Comparison of ipratropium bromide and placebo.
Matera 1996	Time course study over 12 hours on four separate days.
Nardini 1996	Review
Nishimura 1992	Treatment given for two weeks only.
Petro 1981	Short study over 4 weeks not randomised or blinded and measured airways resistance only. Long term study of fenoterol/ipratropium combination over twelve months was uncontrolled, ie pre-post study design.
Pierce 1982	Study conducted in participants with reversible airways disease due to asthma.
Shmelev 1999	Not a randomised controlled trial
Simanenkov 1998	Not a randomised controlled trial
Tang 1984	Study conducted in participants with reversible airways obstruction on three consecutive days.

DATA AND ANALYSES

Comparison 1. Ipratropium bromide versus salmeterol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline FEV1 at 12 weeks	2	458	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.11, -0.00]

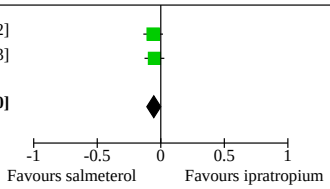
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Change from baseline in FEV1 AUC (12 hour) at 12 weeks	2	454	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.88, 0.32]
3 Change from baseline FVC at 12 weeks	2	458	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.13, 0.12]
4 Change from baseline in FVC AUC (over 12 hours) at 12 weeks	2	454	Mean Difference (IV, Fixed, 95% CI)	0.64 [-0.63, 1.91]
5 HRQL - Chronic Respiratory Disease Questionnaire: change form baseline	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 CRQ- TOTAL DOMAIN	2	467	Mean Difference (IV, Fixed, 95% CI)	-0.58 [-3.50, 2.35]
5.2 CRQ- DYSPNOEA DOMAIN	2	464	Mean Difference (IV, Fixed, 95% CI)	0.85 [-0.15, 1.85]
5.3 CRQ- FATIGUE DOMAIN	2	459	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.89, 0.69]
5.4 CRQ- EMOTION DOMAIN	2	430	Mean Difference (IV, Fixed, 95% CI)	-0.87 [-2.01, 0.27]
5.5 CRQ- MASTERY DOMAIN	2	406	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-1.05, 0.39]
7 Change from baseline in six minute walk distance at 12 weeks	2	471	Mean Difference (IV, Fixed, 95% CI)	10.47 [-1.24, 22.19]
8 Symptom scores-daytime at 12 weeks	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 shortness of breath	2	464	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.25, 0.23]
8.2 cough	2	464	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.34, 0.06]
8.3 chest tightness	2	464	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.23, 0.07]
8.4 change from baseline: shortness of breath	2	535	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.16, 0.07]
8.5 change from baseline: cough	2	535	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.14, 0.06]
8.6 change from baseline: chest tightness	2	535	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.13, 0.02]
9 Symptom scores-nighttime at 12 weeks	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 shortness of breath	2	464	Mean Difference (IV, Fixed, 95% CI)	Not estimable
9.2 cough	2	464	Mean Difference (IV, Fixed, 95% CI)	Not estimable
9.3 chest tightness	2	464	Mean Difference (IV, Fixed, 95% CI)	Not estimable
9.4 change from baseline: shortness of breath	2	535	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.02, 0.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.5 change from baseline: cough	2	535	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.08, 0.10]
9.6 change from baseline: chest tightness	2	535	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.06, 0.05]
9.7 change from baseline: night awakenings	2	535	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.03, 0.15]
10 Rescue bronchodilator use: number of daytime puffs	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 ipratropium versus salmeterol	2	538	Mean Difference (IV, Fixed, 95% CI)	0.34 [-0.20, 0.88]
11 Transitional Dyspnoea Index at end of study	4	1214	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.30, 0.31]
12 Borg Scores for dyspnoea	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 pre-six minute walk test	2	464	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.2 post-six minute walk test	2	464	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.3 Post minus pre six-minute walk test	2	472	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.29, 0.20]
18 Increase in CRQ > or equal to 10 units	2	467	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.77 [0.54, 1.11]
19 Number experiencing one or more COPD exacerbation	2	538	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.84, 1.80]
22 Withdrawals due to adverse events	4	1365	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.82, 2.52]
23 Withdrawals due to lack of efficacy	4	1365	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.61, 1.79]
24 Change in peak expiratory flow (PEF)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
24.1 Morning	2	535	Mean Difference (IV, Fixed, 95% CI)	-10.96 [-16.09, -5.83]
24.2 Evening	2	530	Mean Difference (IV, Fixed, 95% CI)	2.77 [-2.59, 8.14]
25 Increased blood pressure	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
26 Participants with any adverse event	4	1365	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.81, 1.25]

Analysis 1.1. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 1: Change from baseline FEV1 at 12 weeks

Study or Subgroup	ipratropium Mean	SD	Total	salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
Mahler 1999	0.1	0.28	123	0.16	0.32	112	50.4%	-0.06 [-0.14 , 0.02]	+	?
Rennard 2001	0.1	0.27	114	0.15	0.32	109	49.6%	-0.05 [-0.13 , 0.03]	+	+
Total (95% CI)			**237**			**221**	**100.0%**	**-0.06 [-0.11 , -0.00]**		

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Not applicable

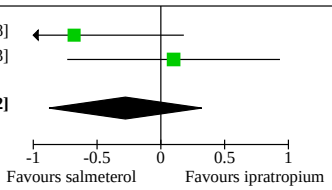


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.2. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 2: Change from baseline in FEV1 AUC (12 hour) at 12 weeks

Study or Subgroup	Ipratropium Mean	SD	Total	Salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
Mahler 1999	1.77	3.42	112	2.45	3.28	122	48.4%	-0.68 [-1.54 , 0.18]	+	?
Rennard 2001	2.11	2.98	113	2.01	3.31	107	51.6%	0.10 [-0.73 , 0.93]	+	+
Total (95% CI)			**225**			**229**	**100.0%**	**-0.28 [-0.88 , 0.32]**		

Heterogeneity: Chi² = 1.63, df = 1 (P = 0.20); I² = 39%
Test for overall effect: Z = 0.91 (P = 0.36)
Test for subgroup differences: Not applicable

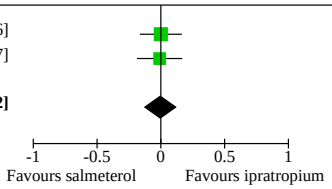


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.3. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 3: Change from baseline FVC at 12 weeks

Study or Subgroup	ipratropium Mean	SD	Total	salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
Mahler 1999	0.03	0.68	112	0.03	0.6	123	53.7%	0.00 [-0.16 , 0.16]	+	?
Rennard 2001	0.25	0.56	114	0.26	0.77	109	46.3%	-0.01 [-0.19 , 0.17]	+	+
Total (95% CI)			**226**			**232**	**100.0%**	**-0.00 [-0.13 , 0.12]**		

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Not applicable

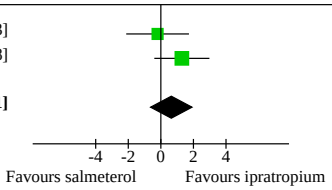


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.4. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 4: Change from baseline in FVC AUC (over 12 hours) at 12 weeks

Study or Subgroup	Ipratropium Mean	SD	Total	Salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
Mahler 1999	3.67	6.46	112	3.87	8.5	122	43.5%	-0.20 [-2.13 , 1.73]	+	?
Rennard 2001	4.41	6.38	113	3.12	6.41	107	56.5%	1.29 [-0.40 , 2.98]	+	+
Total (95% CI)			**225**			**229**	**100.0%**	**0.64 [-0.63 , 1.91]**		

Heterogeneity: Chi² = 1.30, df = 1 (P = 0.25); I² = 23%
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable

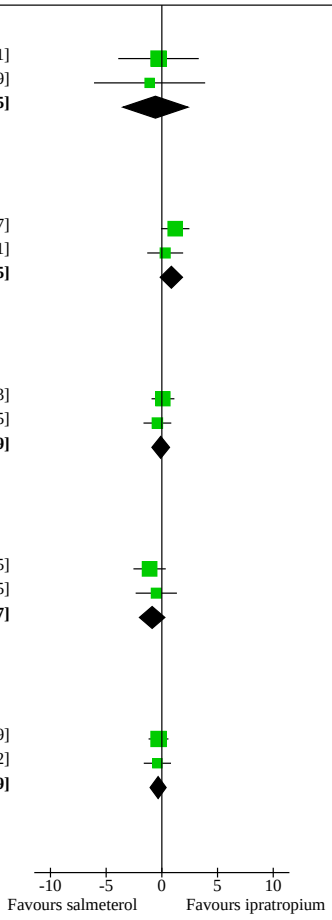


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.5. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 5: HRQL - Chronic Respiratory Disease Questionnaire: change form baseline

Study or Subgroup	Ipratropium Mean	SD	Total	Salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
1.5.1 CRQ- TOTAL DOMAIN										
Mahler 1999	6.8	13.03	118	7.1	15.71	126	65.6%	-0.30 [-3.91 , 3.31]	+	?
Rennard 2001	9.2	19.13	113	10.3	18.88	110	34.4%	-1.10 [-6.09 , 3.89]	+	+
Subtotal (95% CI)			**231**			**236**	**100.0%**	**-0.58 [-3.50 , 2.35]**		
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%										
Test for overall effect: Z = 0.39 (Not estimable)										
1.5.2 CRQ- DYSPNOEA DOMAIN										
Mahler 1999	2.9	5.06	116	1.7	5.05	126	61.5%	1.20 [-0.07 , 2.47]	+	?
Rennard 2001	3.1	6.27	113	2.8	5.98	109	38.5%	0.30 [-1.31 , 1.91]	+	+
Subtotal (95% CI)			**229**			**235**	**100.0%**	**0.85 [-0.15 , 1.85]**		
Heterogeneity: Chi² = 0.74, df = 1 (P = 0.39); I² = 0%										
Test for overall effect: Z = 1.67 (Not estimable)										
1.5.3 CRQ- FATIGUE DOMAIN										
Mahler 1999	1.5	3.97	115	1.4	4.09	122	59.6%	0.10 [-0.93 , 1.13]	+	?
Rennard 2001	2	4.68	113	2.4	4.8	109	40.4%	-0.40 [-1.65 , 0.85]	+	+
Subtotal (95% CI)			**228**			**231**	**100.0%**	**-0.10 [-0.89 , 0.69]**		
Heterogeneity: Chi² = 0.37, df = 1 (P = 0.54); I² = 0%										
Test for overall effect: Z = 0.25 (Not estimable)										
1.5.4 CRQ- EMOTION DOMAIN										
Mahler 1999	2.1	5.3	108	3.2	5.7	113	62.0%	-1.10 [-2.55 , 0.35]	+	?
Rennard 2001	3	6.21	107	3.5	7.37	102	38.0%	-0.50 [-2.35 , 1.35]	+	+
Subtotal (95% CI)			**215**			**215**	**100.0%**	**-0.87 [-2.01 , 0.27]**		
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%										
Test for overall effect: Z = 1.50 (Not estimable)										
1.5.5 CRQ- MASTERY DOMAIN										
Mahler 1999	1	2.94	103	1.3	3.62	107	65.3%	-0.30 [-1.19 , 0.59]	+	?
Rennard 2001	1.8	4.12	101	2.2	4.58	95	34.7%	-0.40 [-1.62 , 0.82]	+	+
Subtotal (95% CI)			**204**			**202**	**100.0%**	**-0.33 [-1.05 , 0.39]**		
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%										
Test for overall effect: Z = 0.91 (Not estimable)										

Test for subgroup differences: Chi² = 5.74, df = 4 (P = 0.22), I² = 30.4%

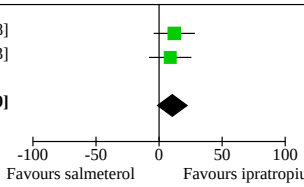


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.7. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 7: Change from baseline in six minute walk distance at 12 weeks

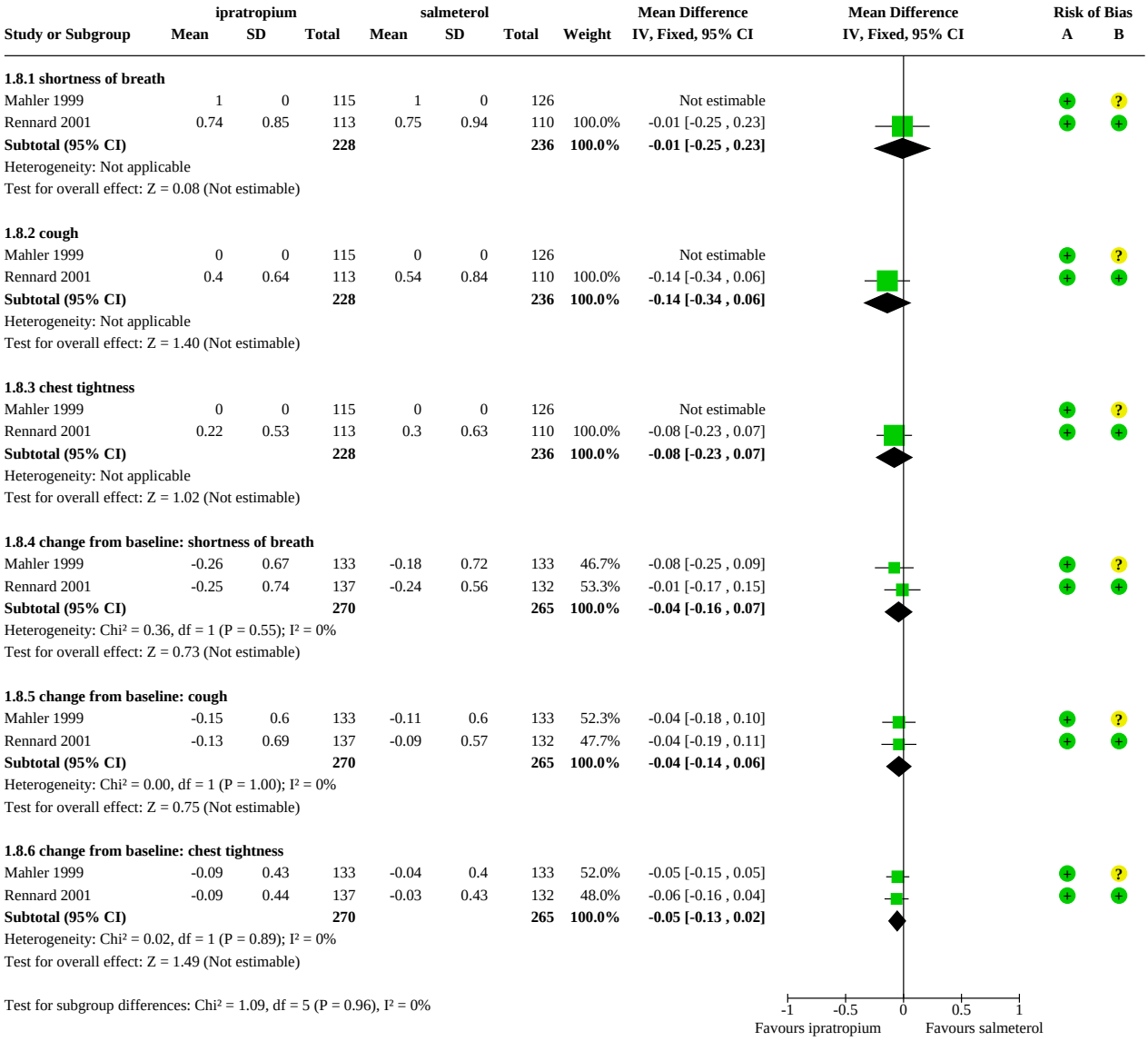
Study or Subgroup	Ipratropium Mean	SD	Total	Salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
Mahler 1999	12.89	68.44	116	0.86	61.61	130	51.4%	12.03 [-4.32 , 28.38]	+	?
Rennard 2001	8.94	64.41	115	0.11	64.16	110	48.6%	8.83 [-7.97 , 25.63]	+	+
Total (95% CI)			**231**			**240**	**100.0%**	**10.47 [-1.24 , 22.19]**		

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.75 (P = 0.08)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.8. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 8: Symptom scores-daytime at 12 weeks



Study or Subgroup	ipratropium Mean	SD	Total	salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
1.8.1 shortness of breath										
Mahler 1999	1	0	115	1	0	126		Not estimable	+	?
Rennard 2001	0.74	0.85	113	0.75	0.94	110	100.0%	-0.01 [-0.25 , 0.23]	+	+
Subtotal (95% CI)			**228**			**236**	**100.0%**	**-0.01 [-0.25 , 0.23]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 0.08 (Not estimable)										
1.8.2 cough										
Mahler 1999	0	0	115	0	0	126		Not estimable	+	?
Rennard 2001	0.4	0.64	113	0.54	0.84	110	100.0%	-0.14 [-0.34 , 0.06]	+	+
Subtotal (95% CI)			**228**			**236**	**100.0%**	**-0.14 [-0.34 , 0.06]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 1.40 (Not estimable)										
1.8.3 chest tightness										
Mahler 1999	0	0	115	0	0	126		Not estimable	+	?
Rennard 2001	0.22	0.53	113	0.3	0.63	110	100.0%	-0.08 [-0.23 , 0.07]	+	+
Subtotal (95% CI)			**228**			**236**	**100.0%**	**-0.08 [-0.23 , 0.07]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 1.02 (Not estimable)										
1.8.4 change from baseline: shortness of breath										
Mahler 1999	-0.26	0.67	133	-0.18	0.72	133	46.7%	-0.08 [-0.25 , 0.09]	+	?
Rennard 2001	-0.25	0.74	137	-0.24	0.56	132	53.3%	-0.01 [-0.17 , 0.15]	+	+
Subtotal (95% CI)			**270**			**265**	**100.0%**	**-0.04 [-0.16 , 0.07]**		
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%										
Test for overall effect: Z = 0.73 (Not estimable)										
1.8.5 change from baseline: cough										
Mahler 1999	-0.15	0.6	133	-0.11	0.6	133	52.3%	-0.04 [-0.18 , 0.10]	+	?
Rennard 2001	-0.13	0.69	137	-0.09	0.57	132	47.7%	-0.04 [-0.19 , 0.11]	+	+
Subtotal (95% CI)			**270**			**265**	**100.0%**	**-0.04 [-0.14 , 0.06]**		
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%										
Test for overall effect: Z = 0.75 (Not estimable)										
1.8.6 change from baseline: chest tightness										
Mahler 1999	-0.09	0.43	133	-0.04	0.4	133	52.0%	-0.05 [-0.15 , 0.05]	+	?
Rennard 2001	-0.09	0.44	137	-0.03	0.43	132	48.0%	-0.06 [-0.16 , 0.04]	+	+
Subtotal (95% CI)			**270**			**265**	**100.0%**	**-0.05 [-0.13 , 0.02]**		
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%										
Test for overall effect: Z = 1.49 (Not estimable)										

Test for subgroup differences: Chi² = 1.09, df = 5 (P = 0.96), I² = 0%

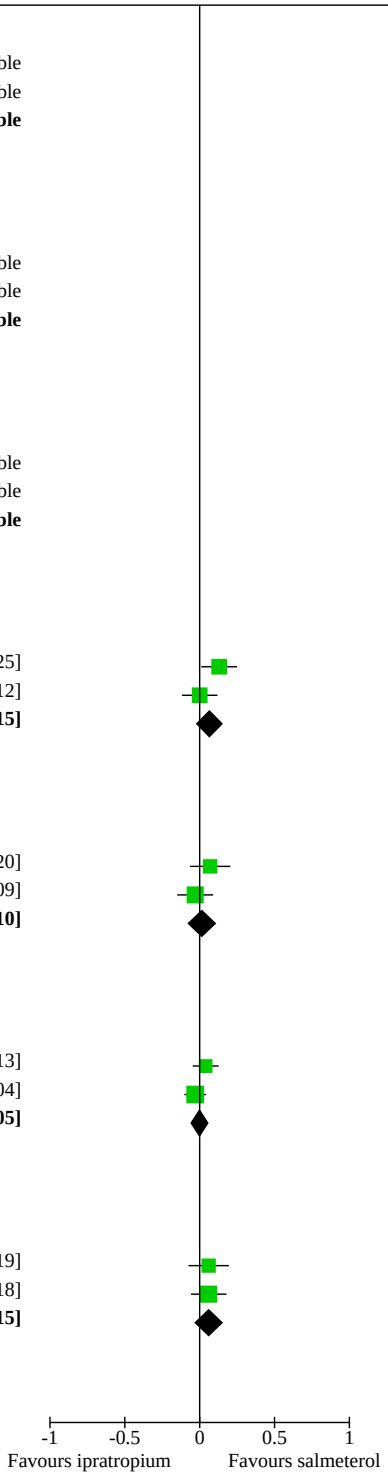
Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

Analysis 1.9. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 9: Symptom scores-nighttime at 12 weeks

Study or Subgroup	ipratropium Mean	ipratropium SD	ipratropium Total	salmeterol Mean	salmeterol SD	salmeterol Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	Risk of Bias B
1.9.1 shortness of breath										
Mahler 1999	0	0	115	0	0	126		Not estimable	+	?
Rennard 2001	0	0	113	0	0	110		Not estimable	+	+
Subtotal (95% CI)			**228**			**236**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										
1.9.2 cough										
Mahler 1999	0	0	115	0	0	126		Not estimable	+	?
Rennard 2001	0	0	113	0	0	110		Not estimable	+	+
Subtotal (95% CI)			**228**			**236**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										
1.9.3 chest tightness										
Mahler 1999	0	0	115	0	0	126		Not estimable	+	?
Rennard 2001	0	0	113	0	0	110		Not estimable	+	+
Subtotal (95% CI)			**228**			**236**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										
1.9.4 change from baseline: shortness of breath										
Mahler 1999	0	0.47	133	-0.13	0.52	133	49.9%	0.13 [0.01 , 0.25]	+	?
Rennard 2001	-0.05	0.46	137	-0.05	0.53	132	50.1%	0.00 [-0.12 , 0.12]	+	+
Subtotal (95% CI)			**270**			**265**	**100.0%**	**0.06 [-0.02 , 0.15]**		
Heterogeneity: Chi² = 2.29, df = 1 (P = 0.13); I² = 56%										
Test for overall effect: Z = 1.51 (Not estimable)										
1.9.5 change from baseline: cough										
Mahler 1999	-0.01	0.59	133	-0.08	0.53	133	44.2%	0.07 [-0.06 , 0.20]	+	?
Rennard 2001	-0.07	0.46	137	-0.04	0.54	132	55.8%	-0.03 [-0.15 , 0.09]	+	+
Subtotal (95% CI)			**270**			**265**	**100.0%**	**0.01 [-0.08 , 0.10]**		
Heterogeneity: Chi² = 1.18, df = 1 (P = 0.28); I² = 15%										
Test for overall effect: Z = 0.31 (Not estimable)										
1.9.6 change from baseline: chest tightness										
Mahler 1999	-0.01	0.37	133	-0.05	0.35	133	41.0%	0.04 [-0.05 , 0.13]	+	?
Rennard 2001	0	0.27	137	0.03	0.33	132	59.0%	-0.03 [-0.10 , 0.04]	+	+
Subtotal (95% CI)			**270**			**265**	**100.0%**	**-0.00 [-0.06 , 0.05]**		
Heterogeneity: Chi² = 1.48, df = 1 (P = 0.22); I² = 33%										
Test for overall effect: Z = 0.05 (Not estimable)										
1.9.7 change from baseline: night awakenings										
Mahler 1999	-0.07	0.52	133	-0.13	0.6	133	43.7%	0.06 [-0.07 , 0.19]	+	?
Rennard 2001	-0.03	0.46	137	-0.09	0.53	132	56.3%	0.06 [-0.06 , 0.18]	+	+
Subtotal (95% CI)			**270**			**265**	**100.0%**	**0.06 [-0.03 , 0.15]**		
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%										
Test for overall effect: Z = 1.32 (Not estimable)										
Test for subgroup differences: Chi² = 2.37, df = 3 (P = 0.50), I² = 0%										



Risk of bias legend

(A) Random sequence generation (selection bias)

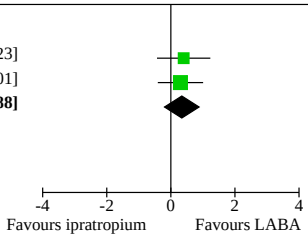
(B) Allocation concealment (selection bias)

Analysis 1.10. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 10: Rescue bronchodilator use: number of daytime puffs

Study or Subgroup	ipratropium Mean	SD	Total	LABA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
1.10.1 ipratropium versus salmeterol											
Mahler 1999	2.4	3.46	133	2	3.49	135	41.9%	0.40 [-0.43 , 1.23]		+	?
Rennard 2001	2.1	2.35	138	1.8	3.45	132	58.1%	0.30 [-0.41 , 1.01]		+	+
Subtotal (95% CI)			**271**			**267**	**100.0%**	**0.34 [-0.20 , 0.88]**			

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.24 (Not estimable)

Test for subgroup differences: Not applicable

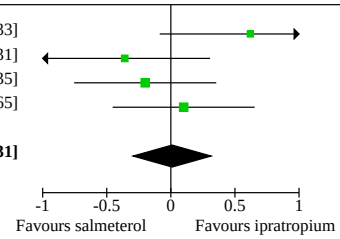


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.11. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 11: Transitional Dyspnoea Index at end of study

Study or Subgroup	Ipratropium Mean	SD	Total	Salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
Mahler 1999	1.26	2.81	117	0.64	2.82	127	18.6%	0.62 [-0.09 , 1.33]		+	?
Rennard 2001	1.07	2.46	114	1.43	2.62	110	20.9%	-0.36 [-1.03 , 0.31]		+	+
SMS40314	1.1	2.72	185	1.3	2.75	189	30.2%	-0.20 [-0.75 , 0.35]		?	?
SMS40315	1.3	2.71	184	1.2	2.74	188	30.3%	0.10 [-0.45 , 0.65]		?	?
Total (95% CI)			**600**			**614**	**100.0%**	**0.01 [-0.30 , 0.31]**			

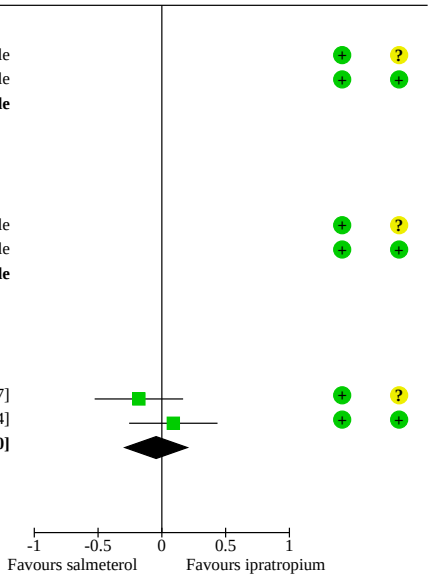
Heterogeneity: Chi² = 4.70, df = 3 (P = 0.20); I² = 36%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.12. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 12: Borg Scores for dyspnoea

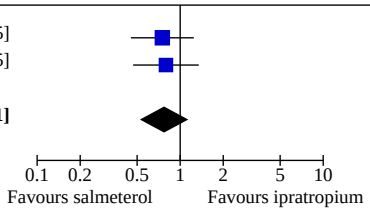
Study or Subgroup	ipratropium Mean	SD	Total	salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
1.12.1 pre-six minute walk test										
Mahler 1999	0	0	115	0	0	126		Not estimable	+	?
Rennard 2001	0	0	113	0	0	110		Not estimable	+	+
Subtotal (95% CI)			**228**			**236**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										
1.12.2 post-six minute walk test										
Mahler 1999	0	0	115	0	0	126		Not estimable	+	?
Rennard 2001	0	0	113	0	0	110		Not estimable	+	+
Subtotal (95% CI)			**228**			**236**		**Not estimable**		
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										
1.12.3 Post minus pre six-minute walk test										
Mahler 1999	-0.31	1.3	117	-0.13	1.48	130	50.0%	-0.18 [-0.53 , 0.17]	+	?
Rennard 2001	-0.08	1.39	115	-0.17	1.26	110	50.0%	0.09 [-0.26 , 0.44]	+	+
Subtotal (95% CI)			**232**			**240**	**100.0%**	**-0.04 [-0.29 , 0.20]**		
Heterogeneity: Chi² = 1.17, df = 1 (P = 0.28); I² = 14%										
Test for overall effect: Z = 0.36 (Not estimable)										
Test for subgroup differences: Not applicable										



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.18. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 18: Increase in CRQ > or equal to 10 units

Study or Subgroup	ipratropium Events	Total	salmeterol Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A	B
Mahler 1999	46	118	58	126	52.1%	0.75 [0.45 , 1.25]	+	?
Rennard 2001	46	113	51	110	47.9%	0.80 [0.47 , 1.35]	+	+
Total (95% CI)		**231**		**236**	**100.0%**	**0.77 [0.54 , 1.11]**		
Total events:	92		109					
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%								
Test for overall effect: Z = 1.39 (P = 0.16)								
Test for subgroup differences: Not applicable								

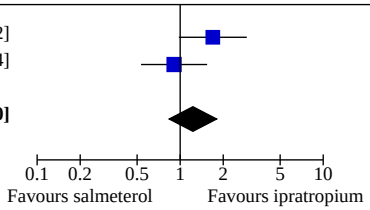


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.19. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 19: Number experiencing one or more COPD exacerbation

Study or Subgroup	ipratropium Events	Total	salmeterol Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A	B
Mahler 1999	41	133	28	135	48.6%	1.69 [0.98 , 2.92]	+	?
Rennard 2001	37	138	38	132	51.4%	0.91 [0.53 , 1.54]	+	+
Total (95% CI)		**271**		**267**	**100.0%**	**1.23 [0.84 , 1.80]**		
Total events:	78		66					

Heterogeneity: Chi² = 2.57, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable

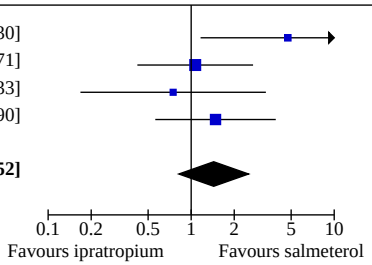


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.22. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 22: Withdrawals due to adverse events

Study or Subgroup	Ipratropium Events	Total	Salmeterol Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A	B
Mahler 1999	7	133	1	135	16.0%	4.74 [1.16 , 19.30]	+	?
Rennard 2001	10	138	9	132	36.3%	1.07 [0.42 , 2.71]	+	+
SMS40314	3	205	4	205	14.1%	0.75 [0.17 , 3.33]	?	?
SMS40315	10	206	7	211	33.5%	1.48 [0.56 , 3.90]	?	?
Total (95% CI)		**682**		**683**	**100.0%**	**1.44 [0.82 , 2.52]**		
Total events:	30		21					

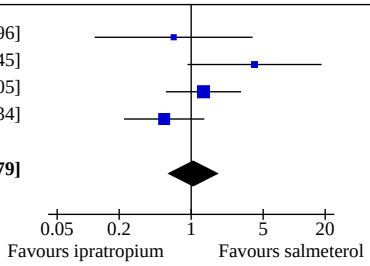
Heterogeneity: Chi² = 3.90, df = 3 (P = 0.27); I² = 23%
Test for overall effect: Z = 1.27 (P = 0.21)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.23. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 23: Withdrawals due to lack of efficacy

Study or Subgroup	Ipratropium Events	Ipratropium Total	Salmeterol Events	Salmeterol Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A	Risk of Bias B
Mahler 1999	2	133	3	135	9.4%	0.68 [0.12 , 3.96]	+	?
Rennard 2001	6	138	1	132	13.0%	4.12 [0.92 , 18.45]	+	+
SMS40314	13	205	10	205	41.4%	1.32 [0.57 , 3.05]	?	?
SMS40315	7	206	13	211	36.3%	0.55 [0.22 , 1.34]	?	?
Total (95% CI)		**682**		**683**	**100.0%**	**1.04 [0.61 , 1.79]**		
Total events:	28		27					

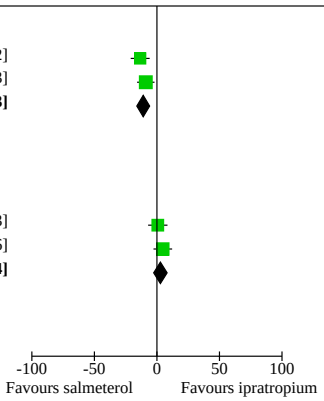


Heterogeneity: Chi² = 5.75, df = 3 (P = 0.12); I² = 48%
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.24. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 24: Change in peak expiratory flow (PEF)

Study or Subgroup	Ipratropium Mean	Ipratropium SD	Ipratropium Total	Salmeterol Mean	Salmeterol SD	Salmeterol Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	Risk of Bias B
1.24.1 Morning										
Mahler 1999	7	32.06	133	20.4	31.02	133	45.8%	-13.40 [-20.98 , -5.82]	+	?
Rennard 2001	6.2	26.1	137	15.1	31.82	132	54.2%	-8.90 [-15.87 , -1.93]	+	+
Subtotal (95% CI)			**270**			**265**	**100.0%**	**-10.96 [-16.09 , -5.83]**		
Heterogeneity: Chi² = 0.73, df = 1 (P = 0.39); I² = 0%										
Test for overall effect: Z = 4.19 (Not estimable)										
1.24.2 Evening										
Mahler 1999	17.3	32.51	132	16.6	31.6	132	48.2%	0.70 [-7.03 , 8.43]	+	?
Rennard 2001	17.9	28.47	135	13.2	33.31	131	51.8%	4.70 [-2.76 , 12.16]	+	+
Subtotal (95% CI)			**267**			**263**	**100.0%**	**2.77 [-2.59 , 8.14]**		
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%										
Test for overall effect: Z = 1.01 (Not estimable)										

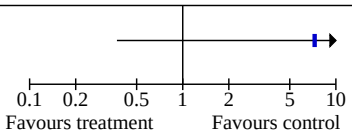


Test for subgroup differences: Chi² = 13.14, df = 1 (P = 0.0003), I² = 92.4%

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.25. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 25: Increased blood pressure

Study or Subgroup	Ipratropium Events	Ipratropium Total	Salmeterol Events	Salmeterol Total	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A	Risk of Bias B
Mahler 1999	3	133	0	135	7.27 [0.37 , 142.09]	+	?

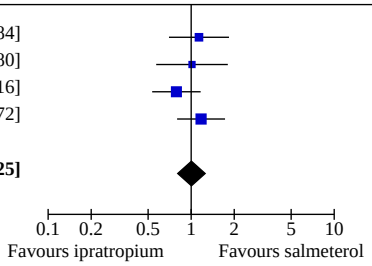


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 1.26. Comparison 1: Ipratropium bromide versus salmeterol, Outcome 26: Participants with any adverse event

Study or Subgroup	Ipratropium Events	Ipratropium Total	Salmeterol Events	Salmeterol Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A	Risk of Bias B
Mahler 1999	78	133	75	135	20.8%	1.13 [0.70 , 1.84]	+	?
Rennard 2001	108	138	103	132	14.6%	1.01 [0.57 , 1.80]	+	+
SMS40314	83	205	95	205	31.9%	0.79 [0.53 , 1.16]	?	?
SMS40315	96	206	90	211	32.6%	1.17 [0.80 , 1.72]	?	?
Total (95% CI)		**682**		**683**	**100.0%**	**1.00 [0.81 , 1.25]**		
Total events:	365		363					

Heterogeneity: Chi² = 2.34, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

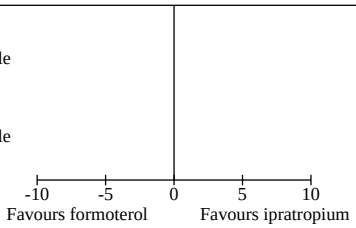
Comparison 2. Ipratropium bromide versus formoterol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absolute pre-dose FEV1 at week 12	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 formoterol 12mcg	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2 formotrol 24mcg	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Rescue bronchodilator use: number of daytime puffs	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 ipratropium versus 12mcg formoterol	1	359	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 ipratropium versus 24mcg formoterol	1	347	Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Change in FEV1(% predicted) from baseline after 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Change in FVC (% predicted) from baseline after 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Change in St Georges Respiratory Questionnaire HRQL (% max score)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Total	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.2 Symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.3 Activity	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.4 Impacts	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Shuttle Walk Test Distance change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Symptom scores (change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Breathlessness -night	1	123	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.01, 0.37]
7.2 Breathlessness -daytime	1	123	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.24, 0.08]
7.3 Cough -night	1	123	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.04, 0.30]
7.4 Cough- daytime	1	123	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.27, 0.11]
7.5 Sleep	1	123	Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.02, 0.32]
8 Absolute SGRQ scores at week 12-formoterol 12mcg	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Total	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.2 Symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.3 Activity	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.4 Impacts	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Absolute SGRQ scores at week 12-formoterol 24mcg	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Total	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.2 Symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.3 Activity	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.4 Impacts	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Ipratropium bromide versus formoterol, Outcome 1: Absolute pre-dose FEV1 at week 12

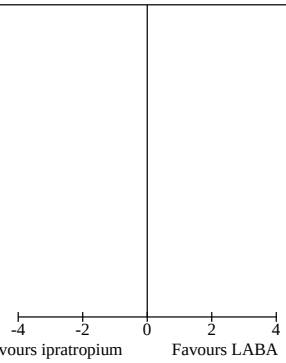
Study or Subgroup	formoterol Mean	SD	Total	ipratropium Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
2.1.1 formoterol 12mcg										
Dahl 2001	1.45	0	181	1.27	0	177	Not estimable		?	?
2.1.2 formotrol 24mcg										
Dahl 2001	1.41	0	169	1.27	0	177	Not estimable		?	?



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 2.2. Comparison 2: Ipratropium bromide versus formoterol, Outcome 2: Rescue bronchodilator use: number of daytime puffs

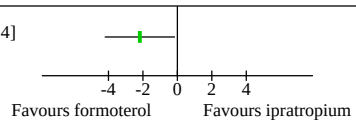
Study or Subgroup	ipratropium Mean	SD	Total	LABA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
2.2.1 ipratropium versus 12mcg formoterol											
Dahl 2001	2	0	178	1.2	0	181		Not estimable		?	?
Subtotal (95% CI)			**178**			**181**		**Not estimable**			
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
2.2.2 ipratropium versus 24mcg formoterol											
Dahl 2001	2	0	178	1.7	0	169		Not estimable		?	?
Subtotal (95% CI)			**178**			**169**		**Not estimable**			
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
Test for subgroup differences: Not applicable											



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 2.3. Comparison 2: Ipratropium bromide versus formoterol, Outcome 3: Change in FEV1(% predicted) from baseline after 3 months

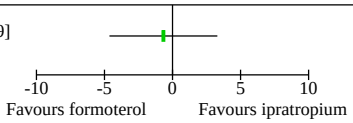
Study or Subgroup	ipratropium Mean	SD	Total	formoterol Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
Stahl 2002	3.35	5.75	62	5.53	5.78	61	-2.18 [-4.22 , -0.14]		+	+



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 2.4. Comparison 2: Ipratropium bromide versus formoterol, Outcome 4: Change in FVC (% predicted) from baseline after 3 months

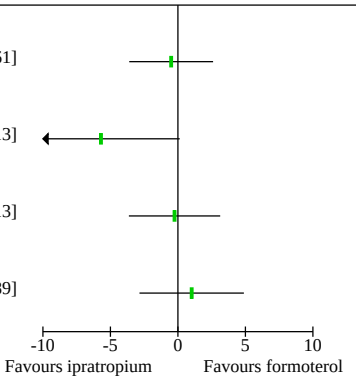
Study or Subgroup	ipratropium Mean	SD	Total	formoterol Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
Stahl 2002	7.07	11.18	62	7.74	11.25	61	-0.67 [-4.63 , 3.29]		+	+



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 2.5. Comparison 2: Ipratropium bromide versus formoterol, Outcome 5: Change in St Georges Respiratory Questionnaire HRQL (% max score)

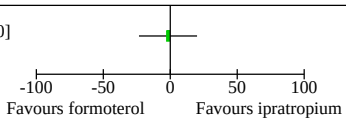
Study or Subgroup	Ipratropium Mean	SD	Total	Formoterol Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
2.5.1 Total										
Stahl 2002	-0.52	8.9	62	-0.02	8.67	61	-0.50 [-3.61 , 2.61]		+	+
2.5.2 Symptoms										
Stahl 2002	-6.26	16.69	62	-0.56	16.32	61	-5.70 [-11.53 , 0.13]		+	+
2.5.3 Activity										
Stahl 2002	-0.89	9.69	62	-0.64	9.45	61	-0.25 [-3.63 , 3.13]		+	+
2.5.4 Impacts										
Stahl 2002	1.55	11.02	62	0.53	10.86	61	1.02 [-2.85 , 4.89]		+	+



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

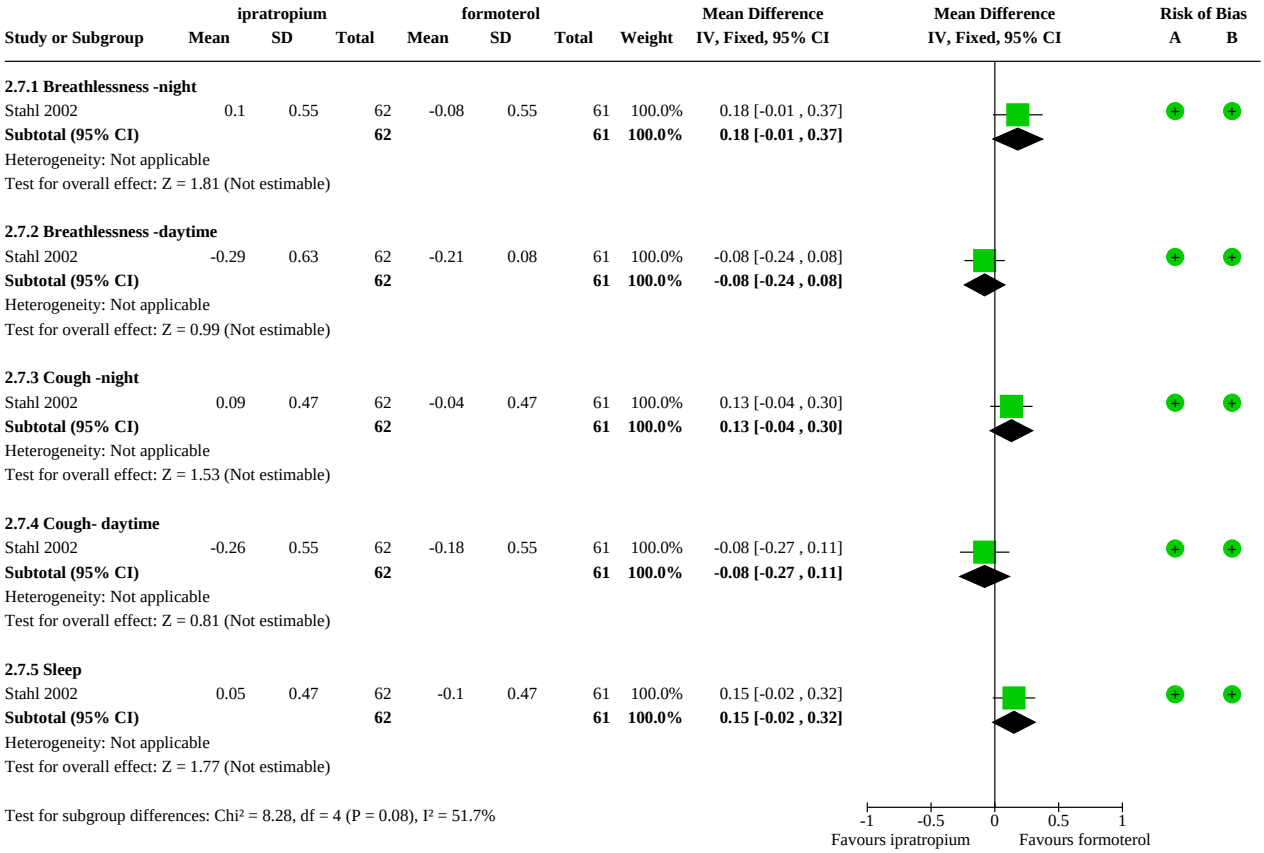
Analysis 2.6. Comparison 2: Ipratropium bromide versus formoterol, Outcome 6: Shuttle Walk Test Distance change from baseline

Study or Subgroup	ipratropium Mean	SD	Total	formoterol Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
Stahl 2002	17.5	60.71	62	19.18	61.94	61	-1.68 [-23.36 , 20.00]		+	+



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 2.7. Comparison 2: Ipratropium bromide versus formoterol, Outcome 7: Symptom scores (change from baseline)

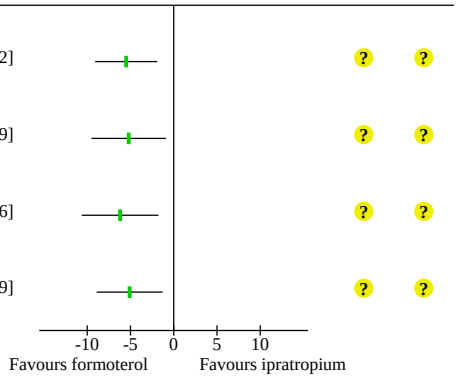


Study or Subgroup	ipratropium Mean	SD	Total	formoterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
2.7.1 Breathlessness -night										
Stahl 2002	0.1	0.55	62	-0.08	0.55	61	100.0%	0.18 [-0.01 , 0.37]	+	+
Subtotal (95% CI)			**62**			**61**	**100.0%**	**0.18 [-0.01 , 0.37]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 1.81 (Not estimable)										
2.7.2 Breathlessness -daytime										
Stahl 2002	-0.29	0.63	62	-0.21	0.08	61	100.0%	-0.08 [-0.24 , 0.08]	+	+
Subtotal (95% CI)			**62**			**61**	**100.0%**	**-0.08 [-0.24 , 0.08]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 0.99 (Not estimable)										
2.7.3 Cough -night										
Stahl 2002	0.09	0.47	62	-0.04	0.47	61	100.0%	0.13 [-0.04 , 0.30]	+	+
Subtotal (95% CI)			**62**			**61**	**100.0%**	**0.13 [-0.04 , 0.30]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 1.53 (Not estimable)										
2.7.4 Cough- daytime										
Stahl 2002	-0.26	0.55	62	-0.18	0.55	61	100.0%	-0.08 [-0.27 , 0.11]	+	+
Subtotal (95% CI)			**62**			**61**	**100.0%**	**-0.08 [-0.27 , 0.11]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 0.81 (Not estimable)										
2.7.5 Sleep										
Stahl 2002	0.05	0.47	62	-0.1	0.47	61	100.0%	0.15 [-0.02 , 0.32]	+	+
Subtotal (95% CI)			**62**			**61**	**100.0%**	**0.15 [-0.02 , 0.32]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 1.77 (Not estimable)										

Test for subgroup differences: Chi² = 8.28, df = 4 (P = 0.08), I² = 51.7%

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

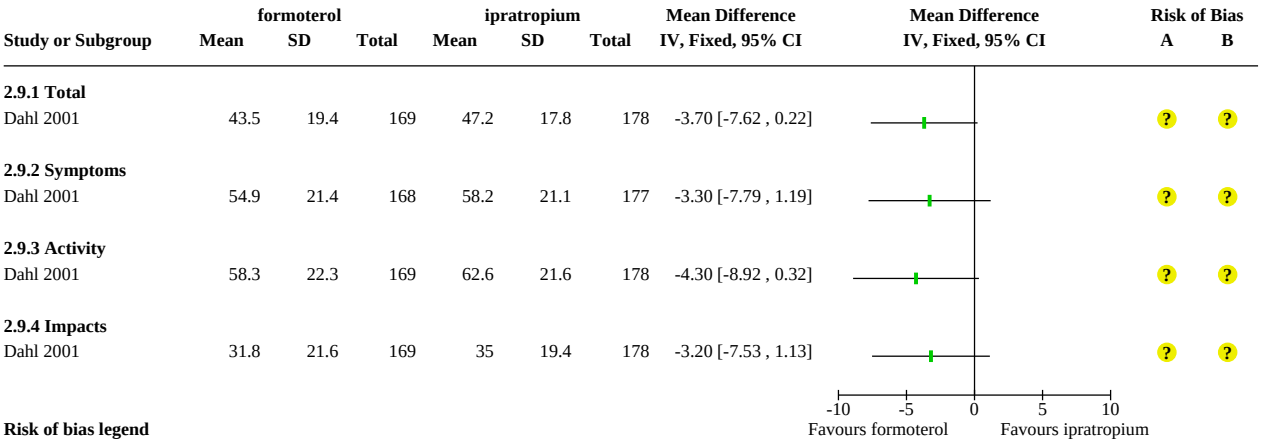
Analysis 2.8. Comparison 2: Ipratropium bromide versus formoterol, Outcome 8: Absolute SGRQ scores at week 12-formoterol 12mcg



Study or Subgroup	formoterol Mean	SD	Total	ipratropium Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
2.8.1 Total									
Dahl 2001	41.7	16.8	181	47.2	17.8	178	-5.50 [-9.08 , -1.92]	?	?
2.8.2 Symptoms									
Dahl 2001	53	20.5	181	58.2	21.1	177	-5.20 [-9.51 , -0.89]	?	?
2.8.3 Activity									
Dahl 2001	56.4	21.3	181	62.6	21.6	178	-6.20 [-10.64 , -1.76]	?	?
2.8.4 Impacts									
Dahl 2001	29.9	17.4	181	35	19.4	178	-5.10 [-8.91 , -1.29]	?	?

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 2.9. Comparison 2: Ipratropium bromide versus formoterol, Outcome 9: Absolute SGRQ scores at week 12-formoterol 24mcg



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

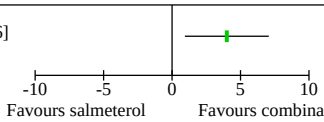
Comparison 3. Ipratropium bromide plus salmeterol versus salmeterol alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1 as a % predicted of day 84 baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Change in FVC as a % predicted of day 84 baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Peak Expiratory Flow (PEF)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Night time PEF	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.2 morning PEF	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Test day HRQL-Chronic Respiratory Disease Questionnaire	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 CRQ- TOTAL DOMAIN	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.2 CRQ- DYSPNOEA DOMAIN	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.3 CRQ- FATIGUE DOMAIN	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4 CRQ- EMOTION DOMAIN	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.5 CRQ- MASTERY DOMAIN	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Test day HRQL- Change in St George's Respiratory Questionnaire (SGRQ)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 SGRQ- TOTAL	3	837	Mean Difference (IV, Fixed, 95% CI)	-2.00 [-3.49, -0.51]
5.2 SRGQ- SYMPTOMS	1	88	Mean Difference (IV, Fixed, 95% CI)	-9.50 [-16.11, -2.89]
5.3 SGRQ- ACTIVITY	1	88	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-7.98, 1.78]
5.4 SGRQ- IMPACTS	1	88	Mean Difference (IV, Fixed, 95% CI)	0.00 [-4.81, 4.81]
6 Daytime Symptom Scores	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7 Rescue bronchodilator use	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 % days with additional salbutamol use	1	94	Mean Difference (IV, Fixed, 95% CI)	-7.00 [-22.24, 8.24]
7.2 % of nights with additional salbutamol use	1	94	Mean Difference (IV, Fixed, 95% CI)	7.00 [-2.84, 16.84]
7.3 Change in supplemental usage (puffs/d)	2	800	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-1.11, -0.23]
8 Number of subjects with at least one exacerbation during 12 week study	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
9 Number of subjects experiencing medication related adverse events	3	936	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.83, 1.40]
10 Summary FEV1 AUC	2	720	Mean Difference (IV, Fixed, 95% CI)	1.38 [0.98, 1.77]
11 TDI at endpoint	2	761	Mean Difference (IV, Fixed, 95% CI)	0.85 [0.46, 1.24]
12 Change in symptom scores	2	815	Mean Difference (IV, Fixed, 95% CI)	-1.89 [-11.11, 7.34]
13 Withdrawals due to lack of efficacy	2	842	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.63 [0.33, 1.20]
14 Withdrawals due to adverse events	2	842	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [0.92, 3.78]

Analysis 3.1. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 1: Change in FEV1 as a % predicted of day 84 baseline

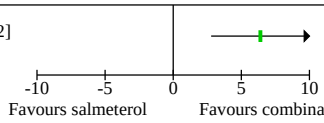
Study or Subgroup	combination Mean	SD	Total	salmeterol Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
van Noord 2000	8.6	8.23	47	4.6	6.86	47	4.00 [0.94 , 7.06]		+	+



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 3.2. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 2: Change in FVC as a % predicted of day 84 baseline

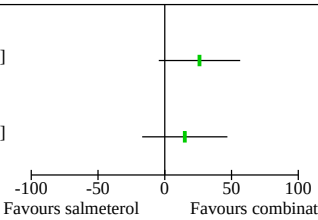
Study or Subgroup	combination Mean	SD	Total	salmeterol Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
van Noord 2000	13.2	9.6	47	6.8	8.23	47	6.40 [2.78 , 10.02]		+	+



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 3.3. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 3: Peak Expiratory Flow (PEF)

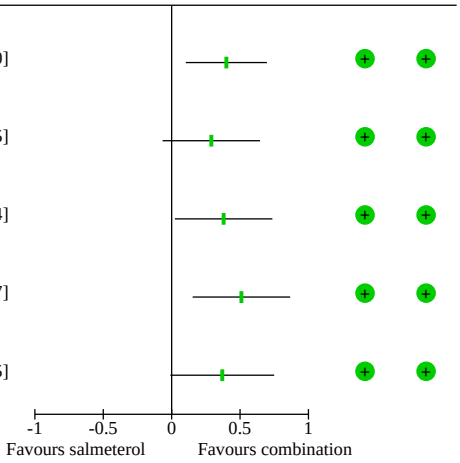
Study or Subgroup	combination Mean	SD	Total	salmeterol Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
3.3.1 Night time PEF										
van Noord 2000	297	75.4	47	271	75.4	47	26.00 [-4.48 , 56.48]		+	+
3.3.2 morning PEF										
van Noord 2000	277	82.3	47	262	75.4	47	15.00 [-16.91 , 46.91]		+	+



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 3.4. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 4: Test day HRQL-Chronic Respiratory Disease Questionnaire

Study or Subgroup	combination Mean	SD	Total	salmeterol Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
3.4.1 CRQ- TOTAL DOMAIN									
van Noord 2000	0.19	0.6	45	-0.21	0.8	43	0.40 [0.10 , 0.70]	+	+
3.4.2 CRQ- DYSPNOEA DOMAIN									
van Noord 2000	0.21	0.8	45	-0.08	0.9	43	0.29 [-0.07 , 0.65]	+	+
3.4.3 CRQ- FATIGUE DOMAIN									
van Noord 2000	0.25	0.8	45	-0.13	0.9	43	0.38 [0.02 , 0.74]	+	+
3.4.4 CRQ- EMOTION DOMAIN									
van Noord 2000	0.17	0.8	45	-0.34	0.9	43	0.51 [0.15 , 0.87]	+	+
3.4.5 CRQ- MASTERY DOMAIN									
van Noord 2000	0.17	0.8	45	-0.2	1	43	0.37 [-0.01 , 0.75]	+	+

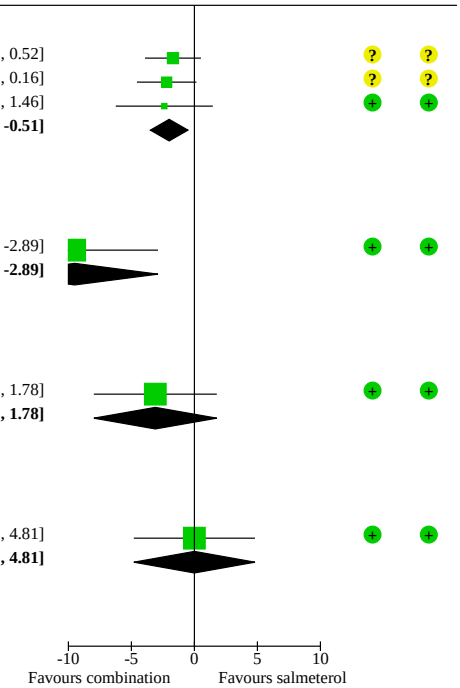


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 3.5. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 5: Test day HRQL- Change in St George's Respiratory Questionnaire (SGRQ)

Study or Subgroup	Combination Mean	SD	Total	salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
3.5.1 SGRQ- TOTAL										
SMS40314	-7.8	11.03	190	-6.1	10.91	186	45.2%	-1.70 [-3.92 , 0.52]	?	?
SMS40315	-7	12.34	188	-4.8	10.88	185	39.9%	-2.20 [-4.56 , 0.16]	?	?
van Noord 2000	-2.4	11	45	-0.01	7.1	43	15.0%	-2.39 [-6.24 , 1.46]	+	+
Subtotal (95% CI)			**423**			**414**	**100.0%**	**-2.00 [-3.49 , -0.51]**		
Heterogeneity: Chi² = 0.14, df = 2 (P = 0.93); I² = 0%										
Test for overall effect: Z = 2.63 (Not estimable)										
3.5.2 SRGQ- SYMPTOMS										
van Noord 2000	-8.1	15.3	45	1.4	16.3	43	100.0%	-9.50 [-16.11 , -2.89]	+	+
Subtotal (95% CI)			**45**			**43**	**100.0%**	**-9.50 [-16.11 , -2.89]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 2.82 (Not estimable)										
3.5.3 SGRQ- ACTIVITY										
van Noord 2000	-2.6	14.5	45	0.5	8.1	43	100.0%	-3.10 [-7.98 , 1.78]	+	+
Subtotal (95% CI)			**45**			**43**	**100.0%**	**-3.10 [-7.98 , 1.78]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 1.25 (Not estimable)										
3.5.4 SGRQ- IMPACTS										
van Noord 2000	-0.5	12.1	45	-0.5	10.9	43	100.0%	0.00 [-4.81 , 4.81]	+	+
Subtotal (95% CI)			**45**			**43**	**100.0%**	**0.00 [-4.81 , 4.81]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 0.00 (Not estimable)										

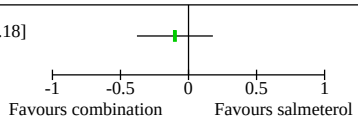
Test for subgroup differences: Chi² = 5.68, df = 3 (P = 0.13), I² = 47.2%



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 3.6. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 6: Daytime Symptom Scores

Study or Subgroup	combination Mean	SD	Total	salmeterol Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
van Noord 2000	1.3	0.69	47	1.4	0.69	47	-0.10 [-0.38 , 0.18]	+	+

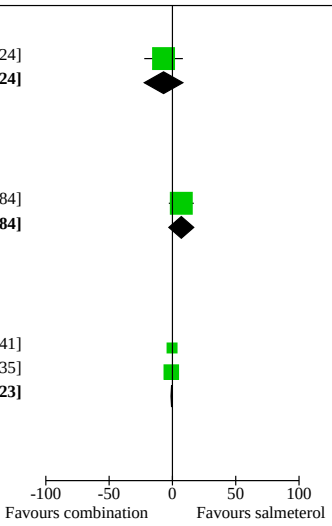


Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 3.7. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 7: Rescue bronchodilator use

Study or Subgroup	combination Mean	SD	Total	salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
3.7.1 % days with additional salbutamol use										
van Noord 2000	27	37.7	47	34	37.7	47	100.0%	-7.00 [-22.24 , 8.24]	+	+
Subtotal (95% CI)			**47**			**47**	**100.0%**	**-7.00 [-22.24 , 8.24]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 0.90 (Not estimable)										
3.7.2 % of nights with additional salbutamol use										
van Noord 2000	24	28.1	47	17	19.9	47	100.0%	7.00 [-2.84 , 16.84]	+	+
Subtotal (95% CI)			**47**			**47**	**100.0%**	**7.00 [-2.84 , 16.84]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 1.39 (Not estimable)										
3.7.3 Change in supplemental usage (puffs/d)										
SMS40314	-3	4.28	204	-2.7	2.78	193	38.1%	-0.30 [-1.01 , 0.41]	?	?
SMS40315	-3.5	2.82	199	-2.6	2.86	204	61.9%	-0.90 [-1.45 , -0.35]	?	?
Subtotal (95% CI)			**403**			**397**	**100.0%**	**-0.67 [-1.11 , -0.23]**		
Heterogeneity: Chi² = 1.72, df = 1 (P = 0.19); I² = 42%										
Test for overall effect: Z = 3.02 (Not estimable)										

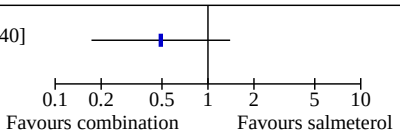


Test for subgroup differences: Chi² = 2.99, df = 2 (P = 0.22), I² = 33.2%

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 3.8. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 8: Number of subjects with at least one exacerbation during 12 week study

Study or Subgroup	combination Events	Total	salmeterol Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A	B
van Noord 2000	6	47	11	47	0.49 [0.17 , 1.40]	+	+

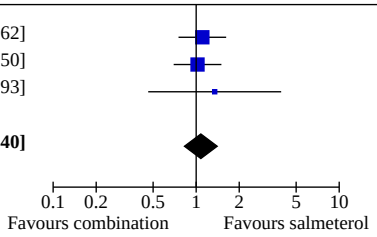


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 3.9. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 9: Number of subjects experiencing medication related adverse events

Study or Subgroup	combination Events	Total	salmeterol Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A	B
SMS40314	104	213	95	205	47.1%	1.10 [0.75 , 1.62]	?	?
SMS40315	92	213	90	211	46.9%	1.02 [0.70 , 1.50]	?	?
van Noord 2000	9	47	7	47	6.0%	1.35 [0.46 , 3.93]	+	+
Total (95% CI)		**473**		**463**	**100.0%**	**1.08 [0.83 , 1.40]**		
Total events:	205		192					

Heterogeneity: Chi² = 0.26, df = 2 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable

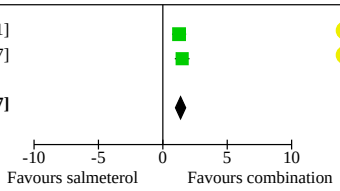


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 3.10. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 10: Summary FEV1 AUC

Study or Subgroup	Combination Mean	SD	Total	Salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
SMS40314	3.4	2.92	179	2.14	2.37	181	51.8%	1.26 [0.71 , 1.81]	?	?
SMS40315	3.31	3.01	184	1.81	2.49	176	48.2%	1.50 [0.93 , 2.07]	?	?
Total (95% CI)			**363**			**357**	**100.0%**	**1.38 [0.98 , 1.77]**		

Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 6.82 (P < 0.00001)
Test for subgroup differences: Not applicable

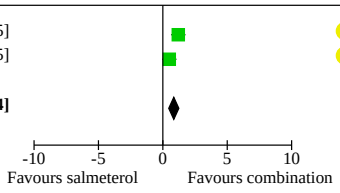


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 3.11. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 11: TDI at endpoint

Study or Subgroup	Combination Mean	SD	Total	Salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
SMS40314	2.5	2.79	194	1.3	2.75	189	50.0%	1.20 [0.65 , 1.75]	?	?
SMS40315	1.7	2.76	190	1.2	2.74	188	50.0%	0.50 [-0.05 , 1.05]	?	?
Total (95% CI)			**384**			**377**	**100.0%**	**0.85 [0.46 , 1.24]**		

Heterogeneity: Chi² = 3.06, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 4.25 (P < 0.0001)
Test for subgroup differences: Not applicable

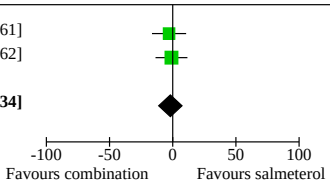


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 3.12. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 12: Change in symptom scores

Study or Subgroup	Combination Mean	SD	Total	Salmeterol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B
SMS40314	-45.4	73.55	208	-42.5	65.29	198	46.6%	-2.90 [-16.41 , 10.61]	?	?
SMS40315	-39.9	67.13	204	-38.9	63	205	53.4%	-1.00 [-13.62 , 11.62]	?	?
Total (95% CI)			**412**			**403**	**100.0%**	**-1.89 [-11.11 , 7.34]**		

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable

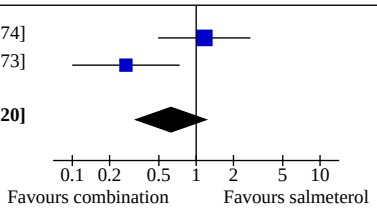


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 3.13. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 13: Withdrawals due to lack of efficacy

Study or Subgroup	Combination Events	Total	Salmeterol Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A	B
SMS40314	12	213	10	205	57.5%	1.16 [0.49 , 2.74]	?	?
SMS40315	3	213	13	211	42.5%	0.27 [0.10 , 0.73]	?	?
Total (95% CI)		**426**		**416**	**100.0%**	**0.63 [0.33 , 1.20]**		
Total events:	15		23					

Heterogeneity: Chi² = 4.71, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Not applicable

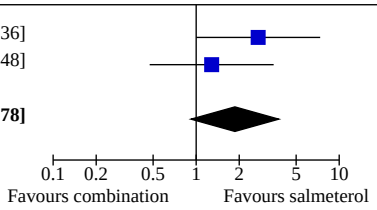


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

Analysis 3.14. Comparison 3: Ipratropium bromide plus salmeterol versus salmeterol alone, Outcome 14: Withdrawals due to adverse events

Study or Subgroup	Combination Events	Total	Salmeterol Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A	B
SMS40314	12	213	4	205	50.0%	2.71 [1.00 , 7.36]	?	?
SMS40315	9	213	7	211	50.0%	1.28 [0.47 , 3.48]	?	?
Total (95% CI)		**426**		**416**	**100.0%**	**1.87 [0.92 , 3.78]**		
Total events:	21		11					

Heterogeneity: Chi² = 1.08, df = 1 (P = 0.30); I² = 7%
Test for overall effect: Z = 1.73 (P = 0.08)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)

FEEDBACK

Error in reporting of P value, March 2008

Summary

On page 11 iii) Dyspnea scores Dahl 2001 reported that F12 produced a significant improvement over IpB in total diary symptom scores (p=0.09) (i.e. P value indicated is not significant) I went back to original article - the value is 0.009.

Reply

We have corrected the P value and thank the submitter for bringing this to our attention

Contributors

Pam McLean-Veysey

WHAT'S NEW

Date	Event	Description
4 July 2008	New search has been performed	Search re-run; no new studies identified
3 July 2008	Feedback has been incorporated	P value corrected following comment from McLean-Veysey P (see Feedback 1)
3 July 2008	Amended	Converted to new review format.

HISTORY

Date	Event	Description
28 March 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

SA: Second draft of protocol, study assessment, data extraction, first draft of review, manuscript revisions
LP: Protocol draft review, study assessment, data extraction, manuscript review
TJ: Protocol draft review, study assessment, data extraction, manuscript review
BA: Manuscript review
BS: Protocol draft review, study assessment
PP: Review editing
JM: First draft of protocol
TL: Write-up and manuscript revisions

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Nederlands Astma Fonds, Netherlands

NOTES

This review has been split from the protocol entitled: Ipratropium bromide versus beta-2 agonists for stable chronic obstructive pulmonary disease. The two reviews focus on slightly different areas of maintenance bronchodilator therapy in COPD. This review focuses on the comparisons between ipratropium bromide and long-acting beta-2 agonists for stable chronic obstructive pulmonary disease.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Agonists [*therapeutic use]; Albuterol [analogs & derivatives] [therapeutic use]; Bronchodilator Agents [*therapeutic use]; Ethanolamines [therapeutic use]; Formoterol Fumarate; Ipratropium [*therapeutic use]; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Randomized Controlled Trials as Topic; Salmeterol Xinafoate

MeSH check words

Adult; Humans